# Stroke: NOACs and statin

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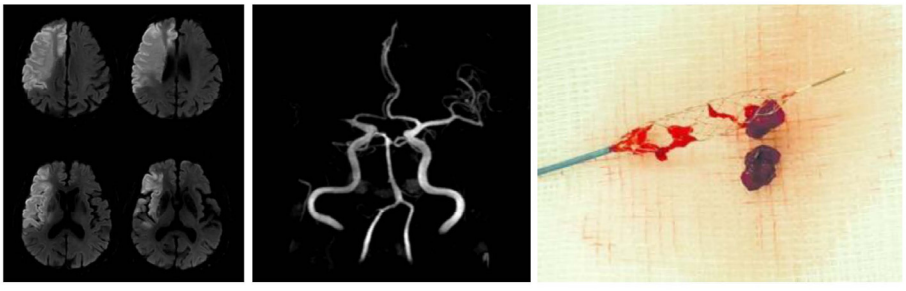
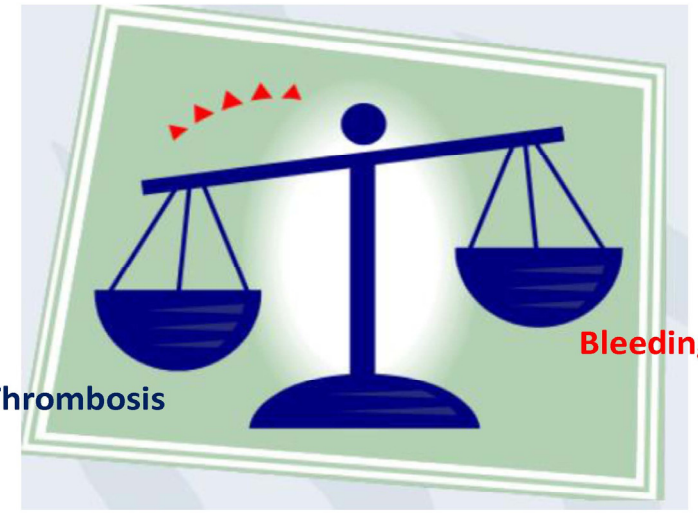
## Stroke is a serious complication of AF

- 3-5 fold higher stroke risk overall
- Without preventive Tx, ischemic stroke in 1/20 patients (5%) per year
- Usually more severe stroke than other stroke subtypes
- Increased the risk of post-stroke mortality

  ➔ OAC reduces the risk of stroke by 64% and risk of death by 26%



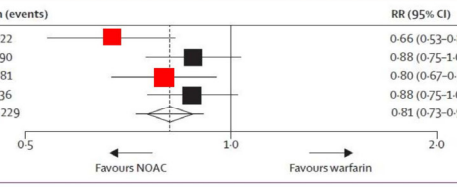
## Anticoagulation: Balance between risk and benefit




## The efficacy and safety of NOACs vs. warfarin in NVAF

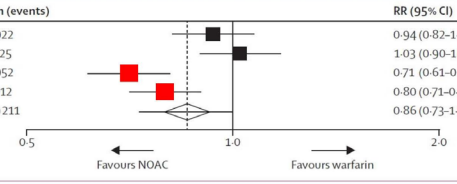
**Stroke or systemic embolic events**

| | NOAC (events) | Warfarin (events) | RR (95% CI) | p |
|---|---|---|---|---|
| RE-LY[5]* | 134/6076 | 199/6022 | 0·66 (0·53–0·82) | 0·0001 |
| ROCKET AF[6]† | 269/7081 | 306/7090 | 0·88 (0·75–1·03) | 0·12 |
| ARISTOTLE[7]‡ | 212/9120 | 265/9081 | 0·80 (0·67–0·95) | 0·012 |
| ENGAGE AF–TIMI 48[8]§ | 296/7035 | 337/7036 | 0·88 (0·75–1·02) | 0·10 |
| Combined (random) | 911/29312 | 1107/29229 | 0·81 (0·73–0·91) | <0·0001 |



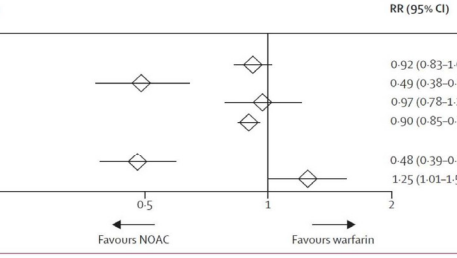

**Major bleeding**

| | NOAC (events) | Warfarin (events) | RR (95% CI) | p |
|---|---|---|---|---|
| RE-LY[5]* | 375/6076 | 397/6022 | 0·94 (0·82–1·07) | 0·34 |
| ROCKET AF[6]† | 395/7111 | 386/7125 | 1·03 (0·90–1·18) | 0·72 |
| ARISTOTLE[7]‡ | 327/9088 | 462/9052 | 0·71 (0·61–0·81) | <0·0001 |
| ENGAGE AF–TIMI 48[8]§ | 444/7012 | 557/7012 | 0·80 (0·71–0·90) | 0·0002 |
| Combined (random) | 1541/29287 | 1802/29211 | 0·86 (0·73–1·00) | 0·06 |




**Secondary efficacy and safety outcomes**

| | Pooled NOAC (events) | Pooled warfarin (events) | RR (95% CI) | p |
|---|---|---|---|---|
| **Efficacy** | | | | |
| Ischaemic stroke | 665/29292 | 724/29221 | 0·92 (0·83–1·02) | 0·10 |
| Haemorrhagic stroke | 130/29292 | 263/29221 | 0·49 (0·38–0·64) | <0·0001 |
| Myocardial infarction | 413/29292 | 432/29221 | 0·97 (0·78–1·20) | 0·77 |
| All-cause mortality | 2022/29292 | 2245/29221 | 0·90 (0·85–0·95) | 0·0003 |
| **Safety** | | | | |
| Intracranial haemorrhage | 204/29287 | 425/29211 | 0·48 (0·39–0·59) | <0·0001 |
| Gastrointestinal bleeding | 751/29287 | 591/29211 | 1·25 (1·01–1·55) | 0·043 |



## Profile of 4NOACs

| | Pradaxa (dabigatran etexilate) | Xarelto (rivaroxaban tablets) | Eliquis (apixaban) tablets | Lixiana (edoxaban tablets) |
|---|---|---|---|---|
| administration | bid | QD<br>With food | bid | QD |
| formulation | capsule | tablet | tablet | tablet |
| CYP metabolism | None | extensive | extensive | <4% |
| Renal elimination | 80% | 35% | 25% | 50% |
| Protein binding | 35% | 92~95% | 87% | 40~59% |
| Pro-drug | Yes | No | No | No |
| Half life | 14~17 hrs | 9~13 hrs | 8~15 hrs | 10~14 hrs |
| T max | 2~3 hrs | 2.5~4 hrs | 3~4 hrs | 1~2 hrs |
| bioavailability | 6~7 % | 60~100 % | 50~60 % | 62% |
| transporter | P-gp | P-gp/BCRP | P-gp/BCRP | P-gp |
| GI tolerability | Dyspepsia 5~10% | No problem | No problem | No problem |

Connolly et al. N Engl J Med 2009;361:1139–1151, Patel et al. N Engl J Med 2011;365:883–891
Granger et al. N Engl J Med 2011;365:981–992 Giugliano et al. N Engl J Med 2013;

## Definition of valvular AF / NOACs indication

- Valvular AF mainly refers to AF patients that have either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves

- 유럽심장학회(ESC) 심방세동 치료 가이드라인
  - 기계판막 치환술을 받은 환자(III, C) 또는
  - 중등도 이상의 승모판막 협착증 환자 (III, C)에게는 NOAC을 추천하지 않음.

| Condition | Eligibility for NOAC therapy |
|---|---|
| Mechanical prosthetic valve | Contraindicated |
| Moderate to severe mitral stenosis (usually of rheumatic origin) | Contraindicated |
| Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.) | Included in NOAC trials |
| Severe aortic stenosis | Limited data (excluded in RE-LY)<br>Most will undergo intervention |
| Bioprosthetic valve (after > 3 months post operatively) | Not advised if for rheumatic mitral stenosis<br>Acceptable if for degenerative mitral regurgitation or in the aortic position |
| Mitral valve repair (after > 3 months post operatively) | Some patients included in some NOAC trials |
| PTAV and TAVI | No prospective data yet<br>May require combination with single or dual antiplatelet therapy |
| Hypertrophic cardiomyopathy | Few data, but patients may be eligible for NOACs |

## $CHA_2DS_2$-VASc score : Anticoagulation in patients with AF

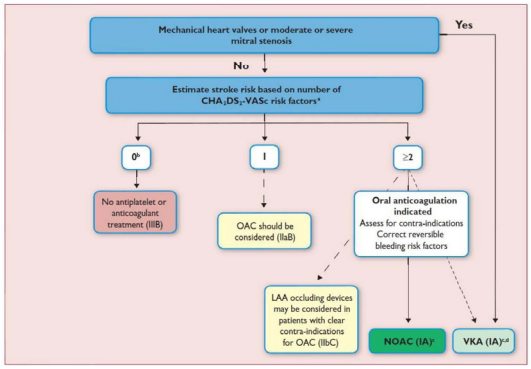
**2016 ESC guideline**

**Table 11** Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism in the $CHA_2DS_2$-VASc score

| $CHA_2DS_2$-VASc risk factor | Points |
|---|---|
| Congestive heart failure<br>Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction | +1 |
| Hypertension<br>Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment | +1 |
| Age 75 years or older | +2 |
| Diabetes mellitus<br>Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin | +1 |
| Previous stroke, transient ischaemic attack, or thromboembolism | +2 |
| Vascular disease<br>Previous myocardial infarction, peripheral artery disease, or aortic plaque | +1 |
| Age 65–74 years | +1 |
| Sex category (female) | +1 |

$CHA_2DS_2$-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

| Recommendations | Class | Level |
|---|---|---|
| The $CHA_2DS_2$-VASc score is recommended for stroke risk prediction in patients with AF | 1 | A |

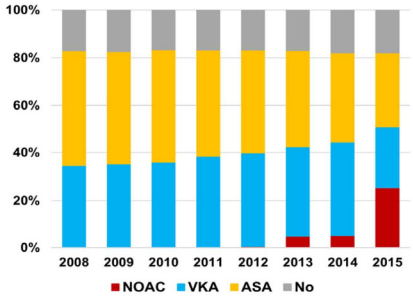



심방세동의 뇌경색 예방을 위해 항혈소판제를 단독으로 사용하는 것은 권장되지 않는다 (class III, level of evidence A)
2018 대한부정맥학회 비판막성 심방세동 환자의 뇌졸중 예방 지침

Eur Heart J 2016;37:2893-2962

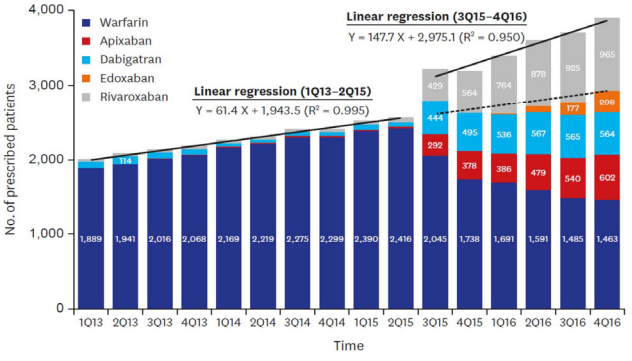
## Trend of OAC prescription among patients with AF in Korea

**A substantial proportion (≈50%) of Korean patients with AF still remain undertreated**



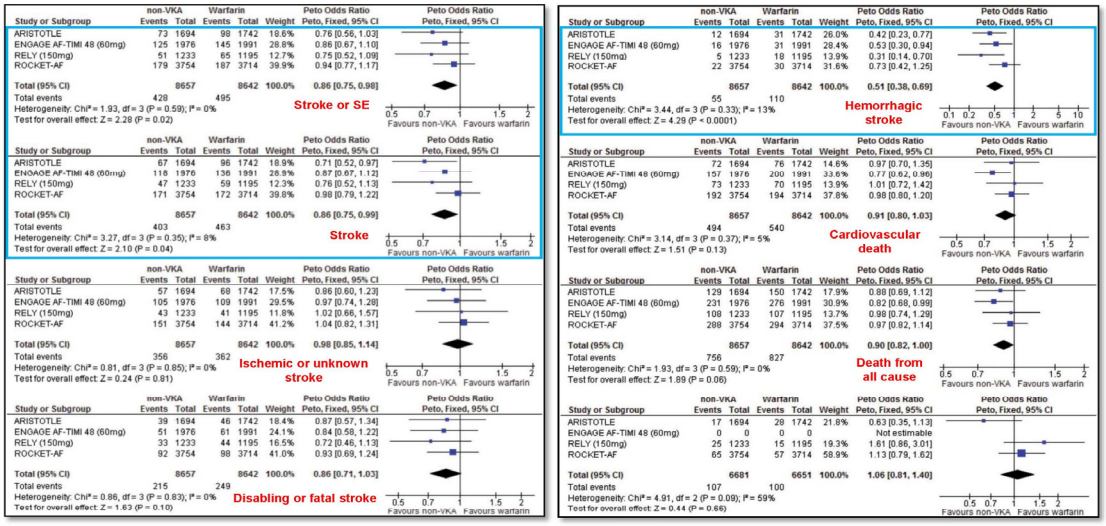

2008 34.7% → 2015 50.6%

Oral anticoagulation Tx




Lee SR et al. PLOS ONE 2017
J Korean Med Sci. 2018;33:e163

## Meta-analysis in patients with AF and previous stroke




Int J of Stroke 2017

European Heart Journal (2017) 38, 860–868
doi:10.1093/eurheartj/ehw069

REVIEW

*Prevention*

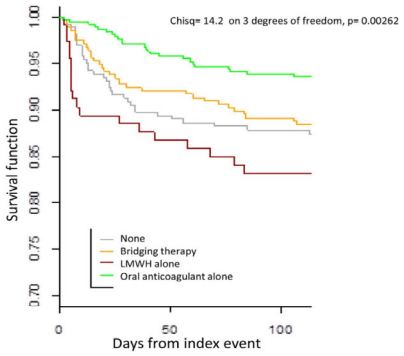
## Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

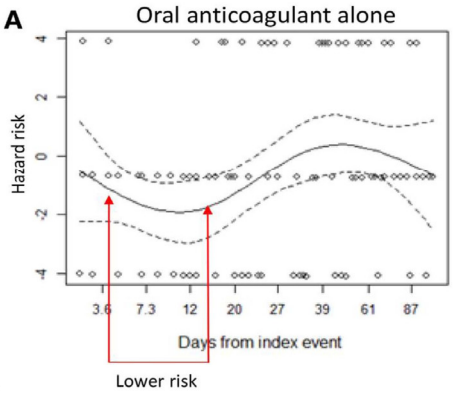
**Heterogeneity tests have found no differences in safety or efficacy among patients with and without prior stroke or TIA**

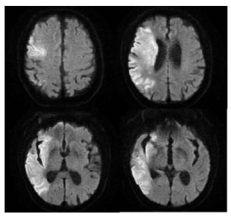
| Secondary Stroke Prevention Recommendation | |
|---|---|
| **First choice** | • NOACs as a group are superior to warfarin for secondary stroke prevention in patients with AF |
| **Comment** | • Aspirin should not be used for secondary stroke prevention in patients with AF<br>• Thre combination of antiplatelet therapy plus OAC in patients with AF dose not prevent major ischemic events better tha dose OAC monotherapy and should be restricted to specific high-risk periods |

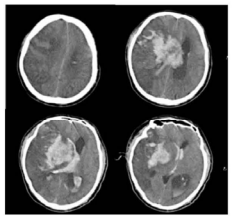
Diener HC et al. Eur Heart J 2017; 38:860-868

## Effect of Anticoagulation and Its Timing: The RAF Study





Early hemorrhagic tranformation

Stroke. 2015;46:2175

## Initiation time of anticoagulation in secondary prevention

**CLASS IIa (MODERATE)** — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

**LEVEL B-NR** — **(Nonrandomized)**

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

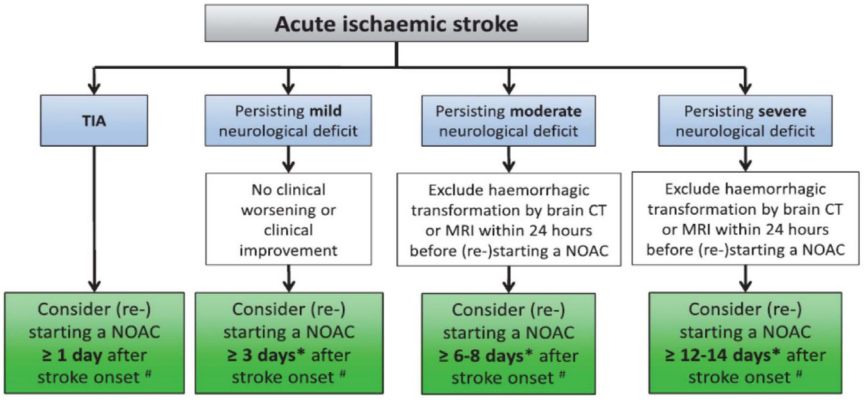
### 2018 AHA/ASA Guideline

| | | |
|---|---|---|
| For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation within 4 to 14 days after the onset of neurological symptoms. | IIa | B-NR |

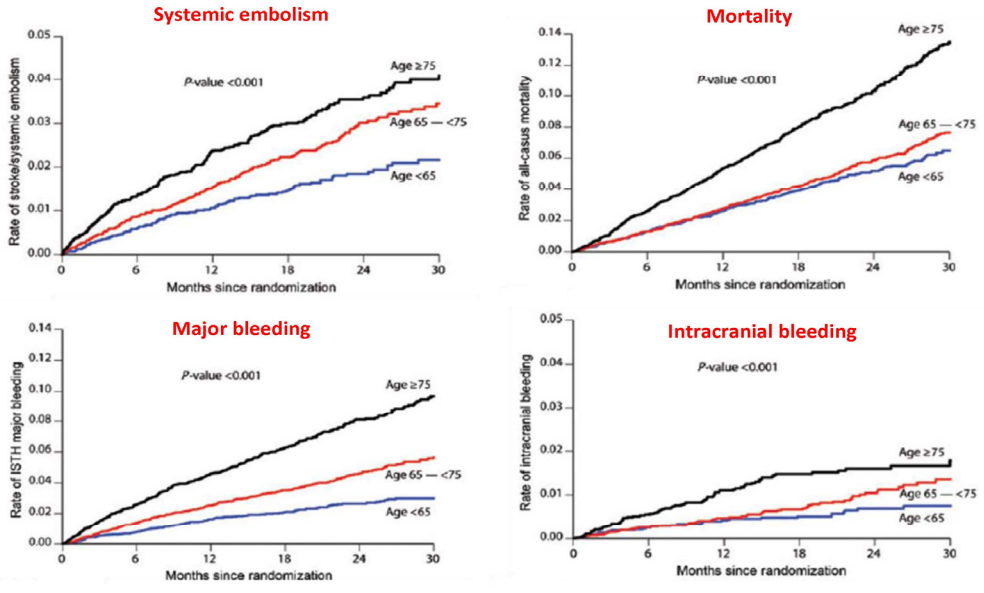
Stroke. 2018;49:e46-e110

## Initiation time of anticoagulation in secondary prevention

**ESC Guidelines** recommend implementation of the 1-3-6-12 rule for initiation or re-initiation of anticoagulation in non-valvular AF patients after acute ischemic stroke

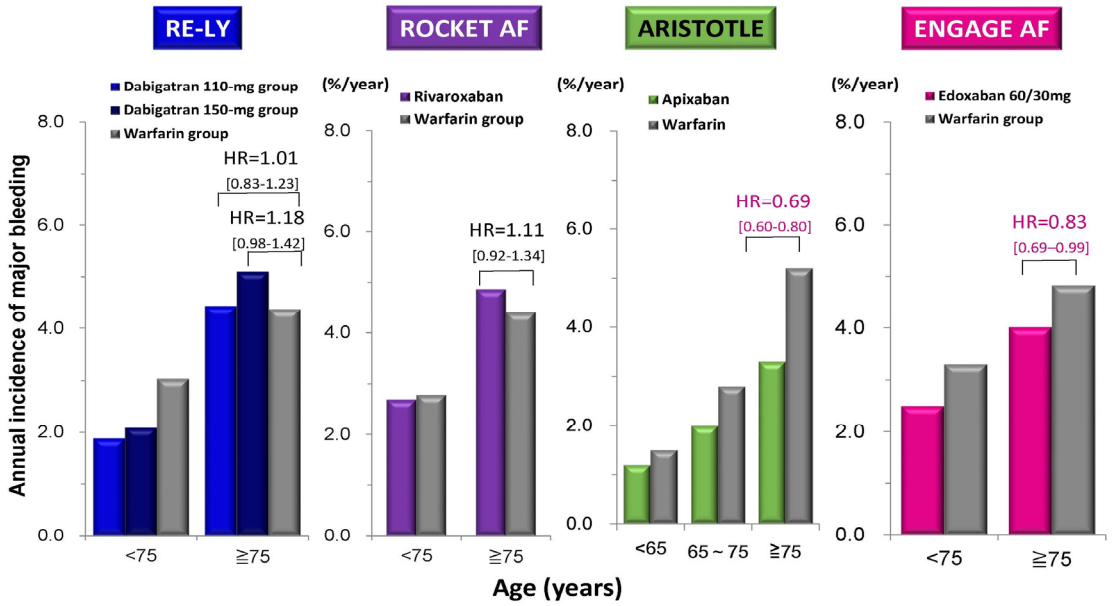



## Stroke/SEE and major bleeding risk according to age




European Heart Journal 2014; 35: 1864–1872.

## NOACs in Elderly Patients (≥75yrs) : major bleeding




Ref) Circulation 2015;132:194-204. Drugs Aging (2016) 33:491–500

## Dose reduction criteria for NOAC

| | Dose reduction criteria | Dose |
|---|---|---|
| Dabigatran | Creatinine clearance 30-50 mL/min | 110 mg bid |
| | P-glycoprotein inhibitors[a] | |
| | Clopidogrel, aspirin, NSAIDs | |
| | Increased bleeding risk[b] | |
| | Age 75 years or more | |
| Rivaroxaban | Age 80 years or more | 15 mg qd |
| | Creatinine clearance 15-50 mL/min[c] | |
| Apixaban | At least two: 1) age 80 years or more, 2) body weight 60 kg or less, 3) creatinine ≥ 1.5 mg/dL | 2.5 mg bid |
| Edoxaban | P-glycoprotein inhibitors[a] | 30 mg qd |
| | Body weight 60 kg or less | |
| | Creatinine clearance 15-50 mL/min[c] | |

NOAC, non-vitamin K antagonist oral anticoagulant; bid, bis in die (twice a day); qd, quaque die (once a day).
[a]P-glycoprotein inhibitors: amiodarone, verapamil, dronedarone, etc.
[b]Increased bleeding risk: coagulopathy, thrombocytopenia, platelet dysfunction, recent major trauma or biopsy, infective endocarditis
[c]Should be used with caution in patients with significant renal impairment (creatinine clearance 15-29 mL/min).

2018 대한부정맥학회 뇌졸중 예방 지침

## NOACs in AF and CKD

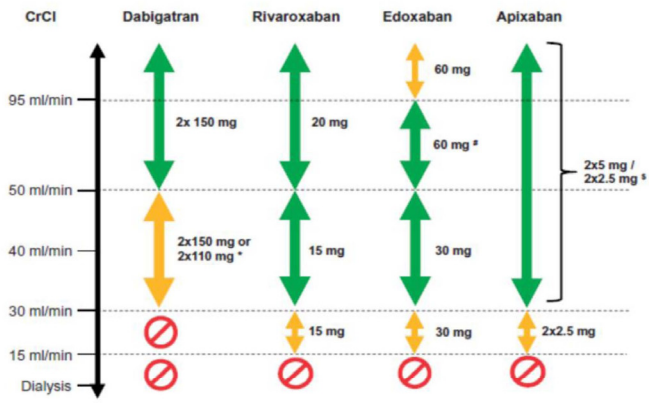
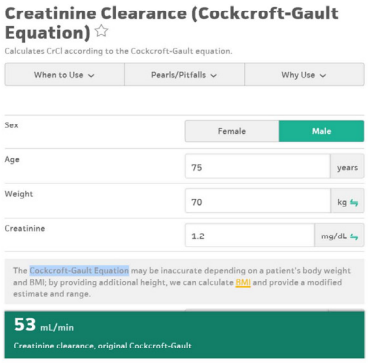



**Figure 4** Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

## Renal function follow-up

Cockcroft-Gault Equation (CrCL)

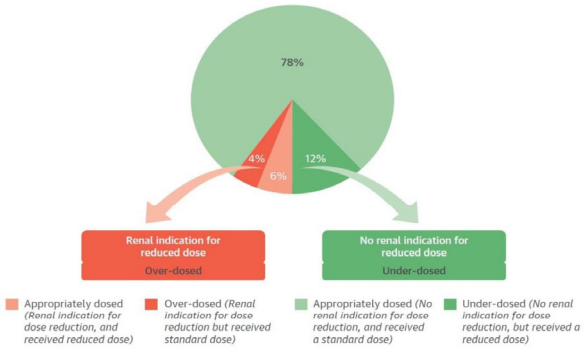
$$= \frac{(140\text{-Age}) \times \text{Mass (in Kilograms)} \times \ [0.85 \text{ if female}]}{72 \text{ X Serum Creatinine (in mg/dL)}}$$

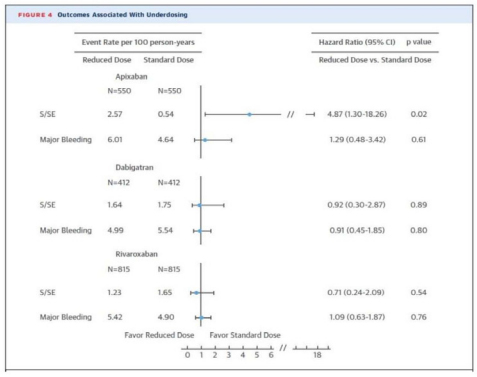


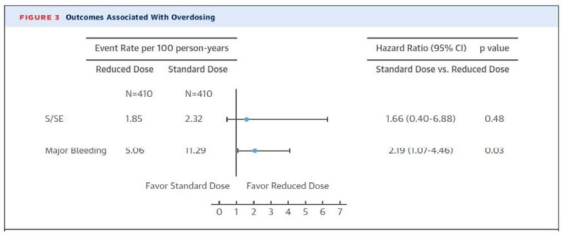

| | |
|---|---|
| Yearly | Haemoglobin, renal and liver function |
| 6-monthly | ≥75–80 years (especially if on dabigatran or edoxaban), or frail |
| x-monthly | If renal function ≤60 mL/min: recheck interval =CrCl/10 |
| On indication | If intercurrent condition that may impact renal or hepatic function |

Updated EHRA Practical Guide Europace 2015

## Inappropriate NOAC dosing and outcomes




JACC 2017;69 : 2779-90

## Mechanisms of NOAC-related GI bleeding

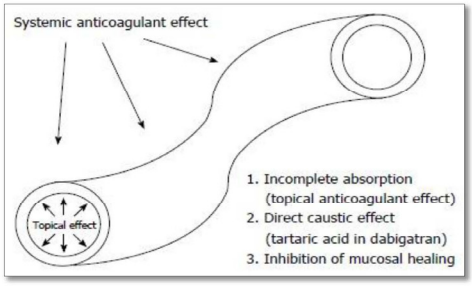



**TABLE 2. Comparison of the absorption and elimination of warfarin, apixaban, dabigatran, and rivaroxaban**

| | Bioavailability | Active anticoagulant present in GI tract | Renal excretion | Hepatic metabolism |
|---|---|---|---|---|
| Warfarin | 100% | None | None | High |
| Dabigatran | 7% | High | High | Low |
| Rivaroxaban | 66% | Moderate | Moderate | Moderate |
| Apixaban | 50% | Moderate | Moderate | Moderate |

KS Cheung, et al. *World J Gastroentrol* 2017; 23:1954

## GI Bleeding of NOAC - Prevention strategies

1. Confirm that NOAC indication is appropriate and that there are no absolute contra-indications to NOAC administration.
2. Confirm that NOAC dosage is appropriate (e.g. dose dabigatran as indicated by creatinine clearance).
3. Screen all patients for presence of on-going GI bleeding by history (history of recent melena or rectal bleeding) and physical exam (digital rectal exam). Consider screening with laboratory testing (faecal occult blood testing, haemoglobin evaluation and evaluation of iron stores). If GI bleeding is suggested, consider GI investigation prior to initiating NOAC treatment.
4. Assess for history of previous GI bleeding and consider diagnostic interventions (e.g. endoscopy) or therapeutic interventions (e.g. concomitant administration of a PPI) where indicated.
5. Assess for co-administration of drugs such as anti-platelet agents or NSAIDs which increase the risk of NOAC related GI bleeding.
6. If patient is concurrently taking anti-platelet medication, weigh the risks, benefits, and alternatives of continuing NOAC plus anti-platelet agent.
7. If patient is taking chronic NSAIDs, consider alternative therapies and/or co-administration of a gastroprotective agent such as a PPI.
8. Consider non-medication risk factors such as alcohol intake, and encourage risk factor modification.
9. Assess creatinine clearance and institute renal protective measures as indicated (especially in patients receiving dabigatran).
10. Counsel the patient regarding the potential for increased risk of GI bleeding in the setting of dehydration, concomitant illness, or concomitant medication use, and the recommended measures in these settings (e.g. seeking prompt medical attention, maintaining hydration, performing laboratory assessments of renal function).

Desai et al. New oral anticoagulants and GI bleeding. Thromb Haemost 2013; 110: 205–212

## Initiation of NOACs after GI bleeding

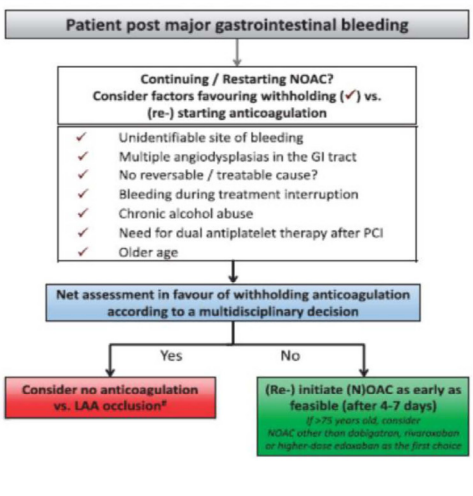



**Figure 7** (Re-) initiation of anticoagulation post-gastrointestinal bleeding. #Without evidence; ideally include patient in ongoing trial.

## How to deal with dosing errors?

- Missed dose
  - 약물복용 시간간격 (12 hours or 24 hours) 기준으로 약을 복용하지 않은 것을 안 시점에서 ½ 이 경과하지 않은 경우 약물 복용하도록 ½ 이상 지난 경우는 생략하고 다음 예정 복용시간에 약을 복용하게 함

- Double dose
  - 약을 두배로 복용한 경우, BID 용법인 경우는 다음 예정약 복용을 생략하고, QD 용법인 경우는 24시간 후에 다시 정상 용량을 복용

- Uncertainty about dose intake
  - BID dosing regimen : 다음 예정약을 복용한다
  - OD dosing regimen
    - : $CHA_2DS_2$-VASc ≥3 경우 바로 복용.
    - : $CHA_2DS_2$-VASc ≤2 경우 기다렸다가 다음 예정 복용약 복용

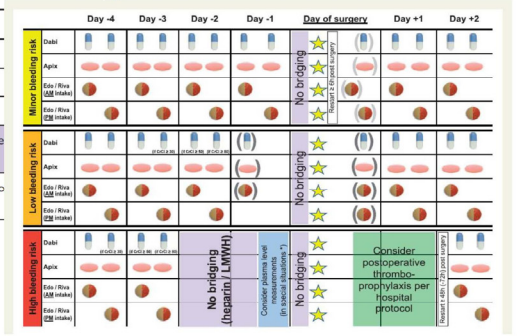
## When to stop and restart NOACs?

**Classification of elective surgical interventions according to bleeding risk**

**Table 12** Classification of elective surgical interventions according to bleeding risk

| |
|---|
| Interventions with minor bleeding risk |
| Dental interventions |
| Extraction of 1–3 teeth |
| Paradontal surgery |
| Incision of abscess |
| Implant positioning |
| Cataract or glaucoma intervention |
| Endoscopy without biopsy or resection |
| Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .) |
| Interventions with low bleeding risk (i.e. infrequent or with low clinical impact) |
| Endoscopy with biopsy |
| Prostate or bladder biopsy |
| Electrophysiological study or catheter ablation (except complex procedures, see below) |
| Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section) |
| Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease) |

| |
|---|
| Interventions with high bleeding risk (i.e. frequent and/or with high impact) |
| Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.) |
| Spinal or epidural anaesthesia; lumbar diagnostic puncture |
| Thoracic surgery |
| Abdominal surgery |
| Major orthopaedic surgery |
| Liver biopsy |
| Transurethral prostate resection |
| Kidney biopsy |
| Extracorporeal shockwave lithotripsy (ESWL) |
| Interventions with high bleeding risk AND increased thromboembolic risk |
| Complex left-sided ablation (pulmonary vein isolation ablations) |

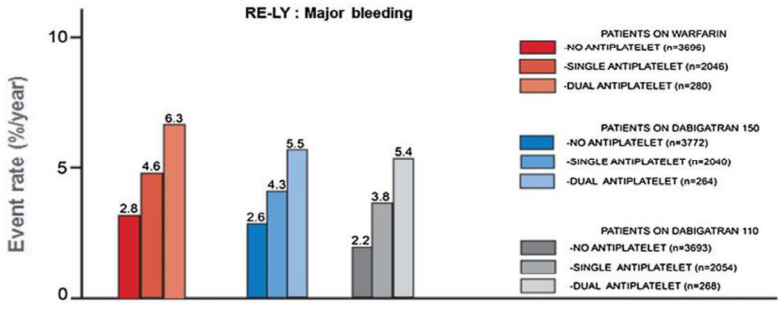


## When to stop and restart NOACs?

**Table 11** Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

| | Dabigatran | | Apixaban – Edoxaban – Rivaroxaban | |
|---|---|---|---|---|
| | No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake) | | | |
| | Low risk | High risk | Low risk | High risk |
| CrCl ≥80 mL/min | ≥24 h | ≥48 h | ≥24 h | ≥48 h |
| CrCl 50–79 mL/min | ≥36 h | ≥72 h | ≥24 h | ≥48 h |
| CrCl 30–49 mL/min | ≥48 h | ≥96 h | ≥24 h | ≥48 h |
| CrCl 15–29 mL/min | Not indicated | Not indicated | ≥36 h | ≥48 h |
| CrCl <15 mL/min | No official indication for use | | | |
| **No bridging with LMWH/UFH** | | | | |
| Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high-bleeding risk interventions (see also *Figure 8*) | | | | |
| Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication) | | | | |

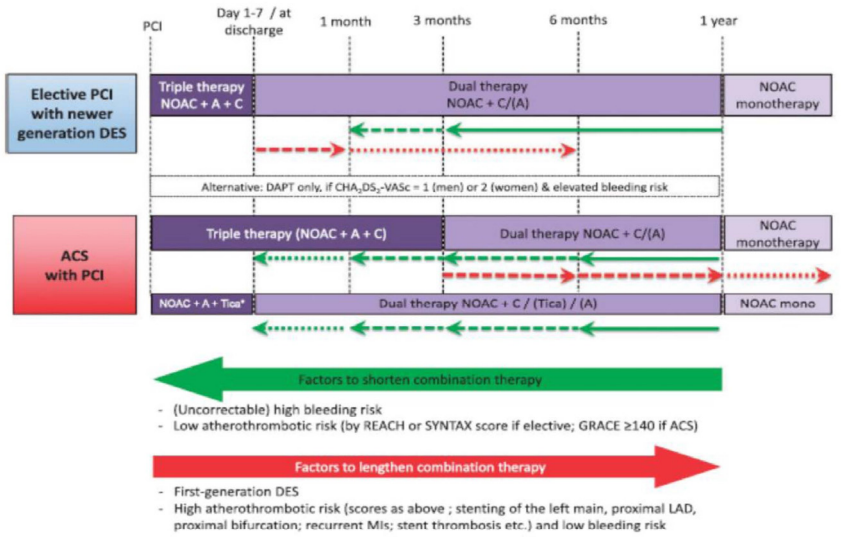
## Concomitant Use of Antiplatelet with Anticoagulation



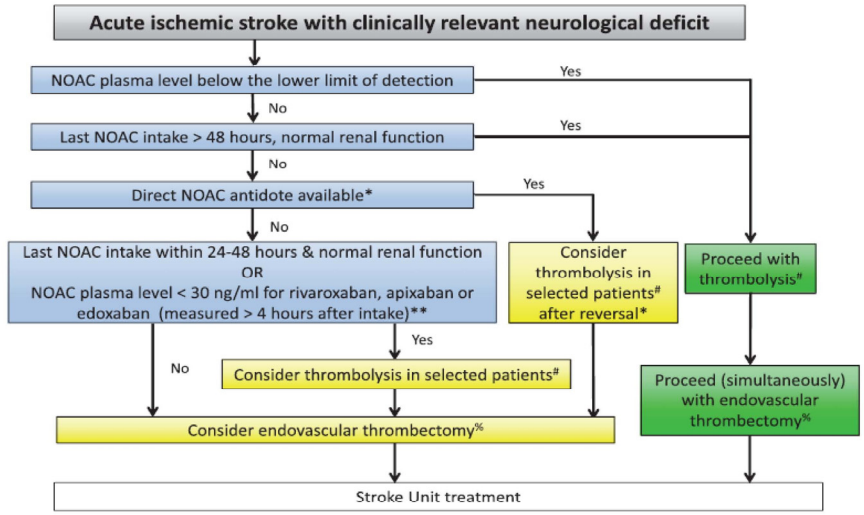

| | Class of Recommendation | Level of Evidence |
|---|---|---|
| Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition. | III | B |

Circulation 2013;127:634

## OAC Tx after coronary intervention in AF patients

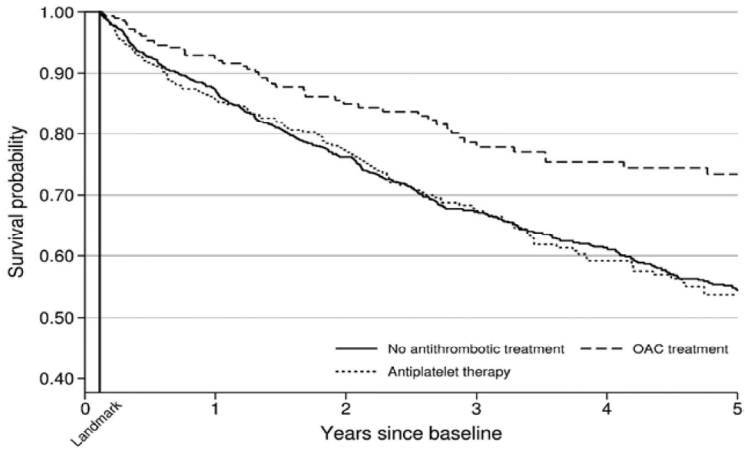



## Treatment of acute ischemic stroke in a patient on NOACs



## Follow-up of ICH patients with atrial fibrillation

Danish nationwide registries in the period between 1997 and 2013



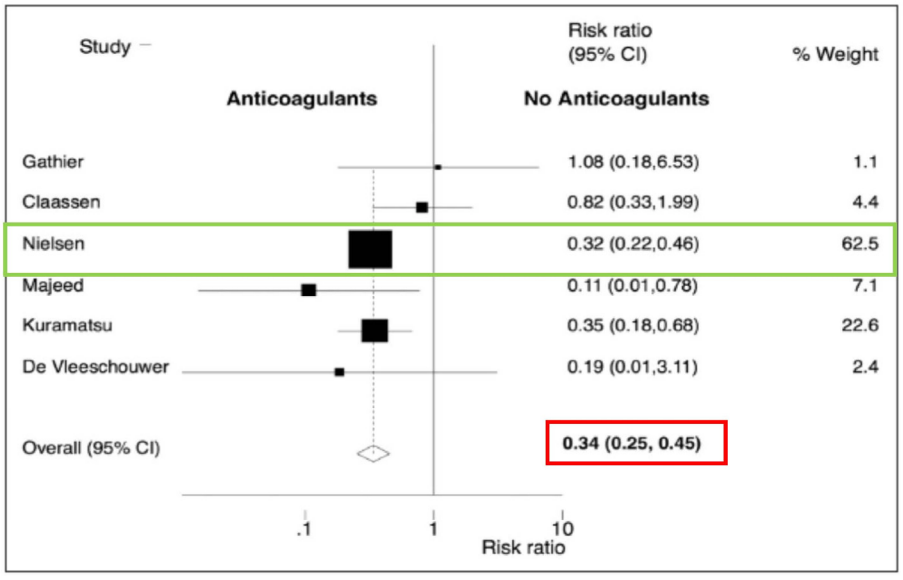

**Oral anticoagulation**

**None**
**Antiplatelet Tx**

Circulation. 2015;132:517-

## Restarting Anticoagulant Therapy After ICH

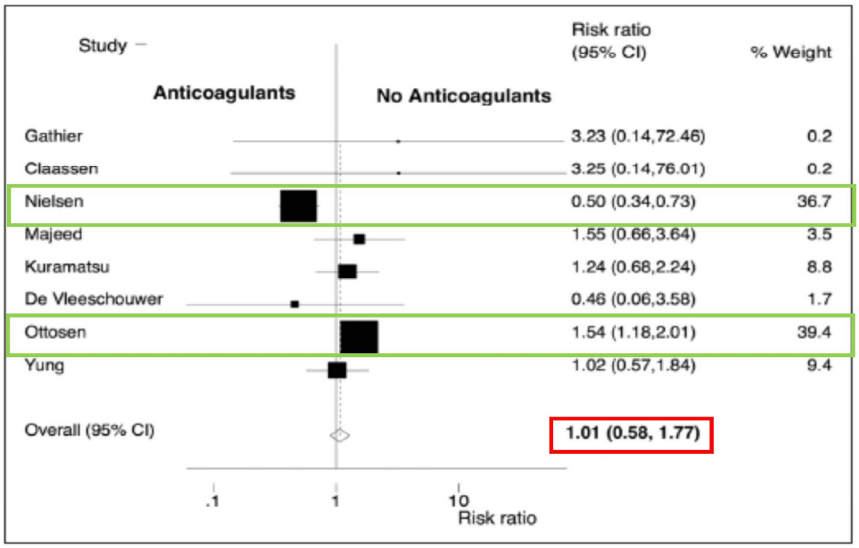
**Arterial thromboembolic complications**




Stroke. 2017;48:1594-1600.

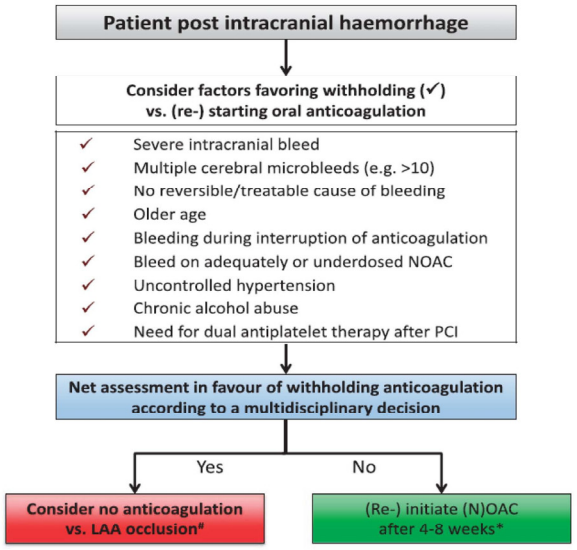
## Restarting Anticoagulant Therapy After ICH

**Recurrence of intracranial hemorrhage**




Stroke. 2017;48:1594-1600.

## Initiation of anticoagulation after ICH




European Heart Rhythm Association Practical Guide. European Heart Journal 2018

# Ischemic Stroke : Statin

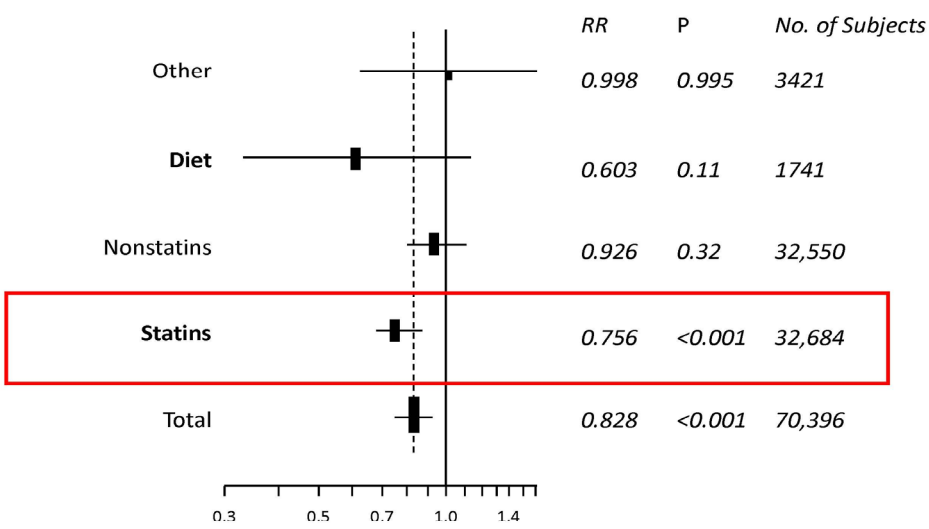
Dae-Hyun Kim, MD.
Cardiocerebrovascular Center
Department of Neurology, Dong-A University Hospital

## Statin and stroke prevention

- Statin for primary stroke prevention
- High dose statin and beyond LDL lowering effect
- Statin in acute stroke phase
- Statin for secondary stroke prevention

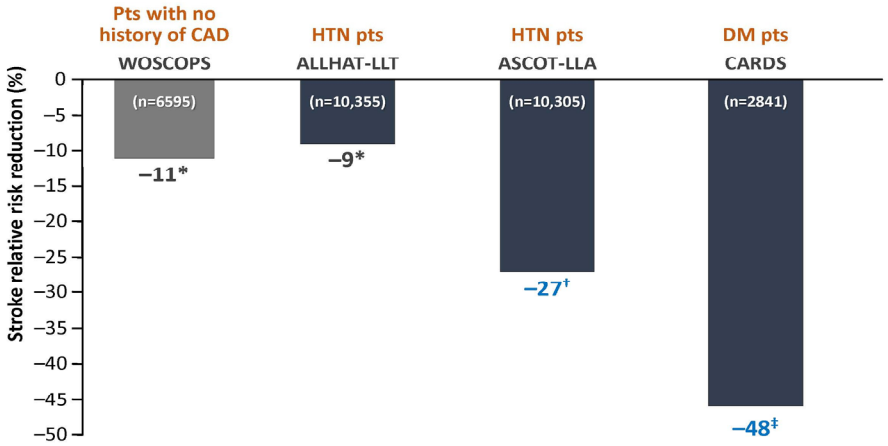
## Statin for primary stroke prevention

## Cholesterol lowering and stroke risk: not equally effective



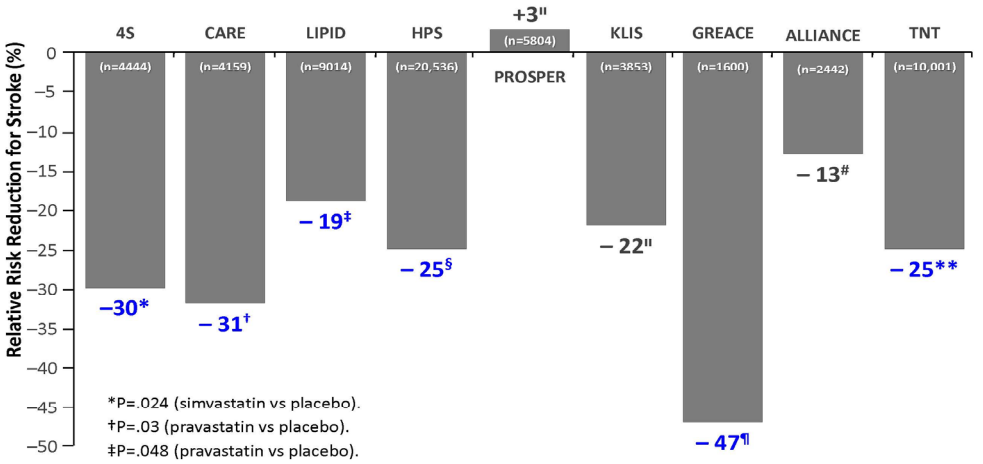

Corvol JC et al. Arch Intern Med 2003;163:669-676

## Primary prevention of Stroke by Statins in Patients without CHD



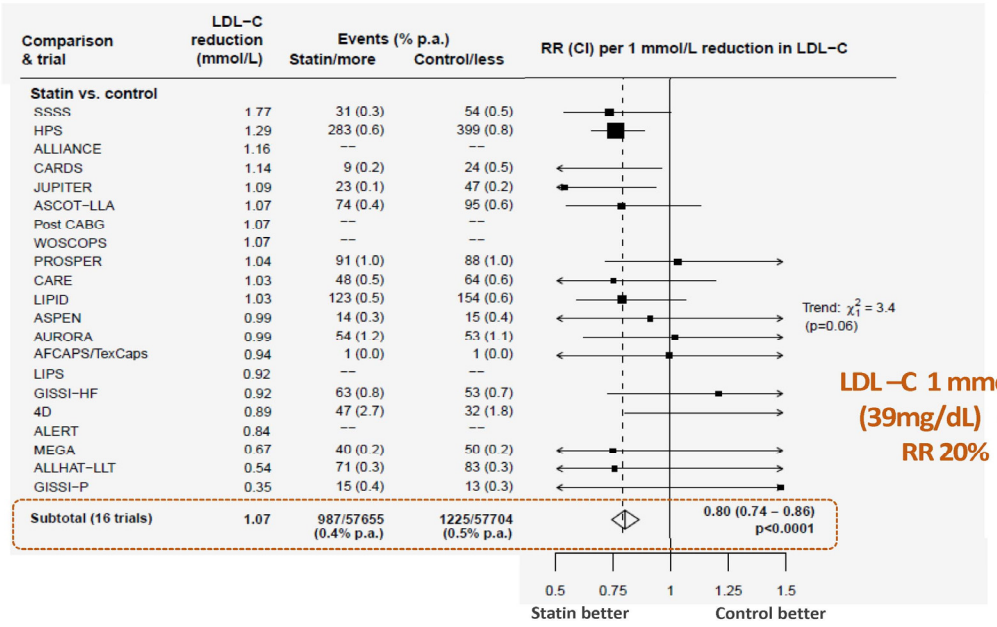

*P = NS (pravastatin vs placebo or usual care).
†P = .024 (atorvastatin vs placebo).
‡P = not reported (atorvastatin vs placebo).

## Primary prevention of Stroke by Statins in Patients with CHD




*P=.024 (simvastatin vs placebo).
†P=.03 (pravastatin vs placebo).
‡P=.048 (pravastatin vs placebo).
§P<.0001 (simvastatin vs placebo).
"P=NS (pravastatin vs placebo or conventional treatment).
¶P=.034 (atorvastatin vs usual care).
#P=NS (atorvastatin vs usual care).
**P=.02 (80 mg vs 10 mg atorvastatin).

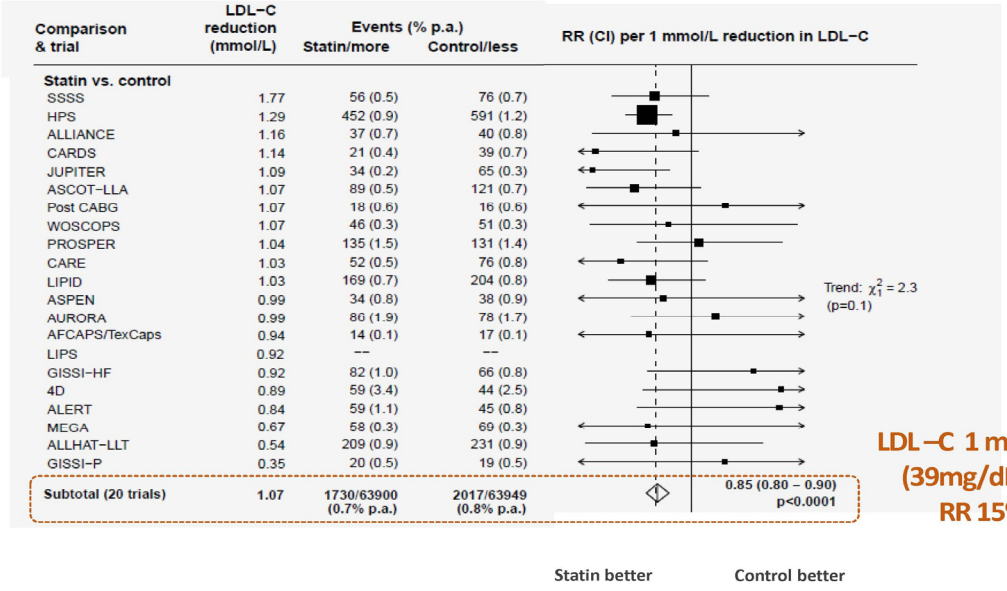
## Effect on ISCHEMIC stroke by Statins (Meta-analysis)




LDL–C 1 mmol/L (39mg/dL) ↓, RR 20%

CTT Collaboration. Lancet 2010;376:1670-1681.

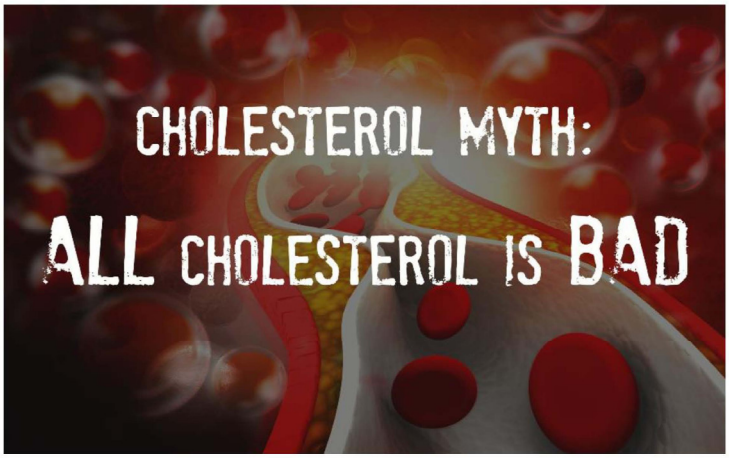
## Effect on ANY stroke by Statins (Meta-analysis)




LDL–C 1 mmol/L (39mg/dL )↓, RR 15%

CTT Collaboration. Lancet 2010;376:1670-1681

## Statin and cardiovascular disease



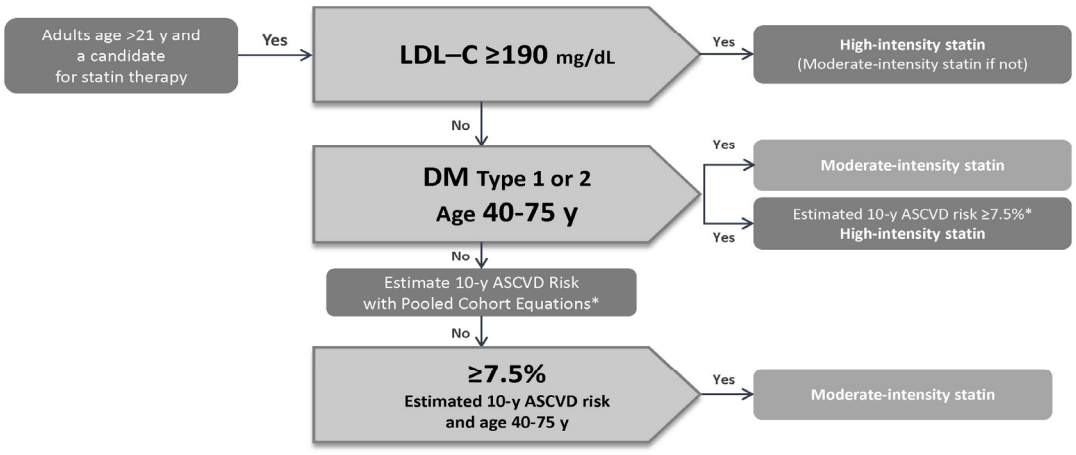

Statins in the drinking water

Dr. Gary Huber

Statins in the drinking water

Statins in the drinking water? We are getting closer to absolute lunacy as another report came out suggesting that anyone over the age of 40 with 1 risk factor for heart disease should automatically be placed on a statin cholesterol lowering drug. Interestingly the report suggests not doing this to folks OVER the age of 75. That's because these drugs cause increased risk for diabetes, loss of coenzyme Q10, liver toxicity and cognitive decline, which is accelerated in older people.

## 2013 ACC/AHA guideline – 4 statin benefit group

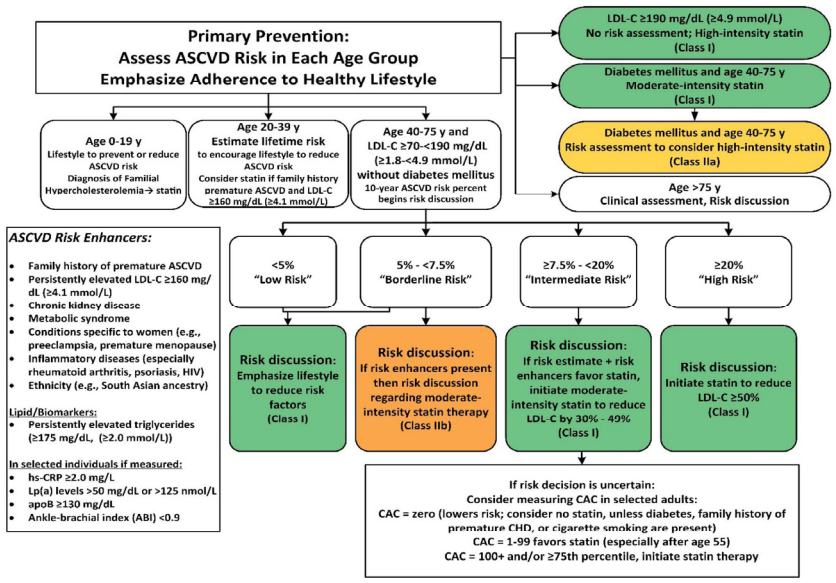



http://my.americanheart.org/cvriskcalculator/

Age, Sex, Race, Total chol, HDL, SBP, HT Tx, DM, Smoking

Stone NJ et al. Circulation 2013

## 2018 American Lipid Guidelines for Primary Prevention




Circulation 2018

## Intensity of Statin Therapy and LDL-c reduction

| Intensity | High-Intensity | Moderate-Intensity | Low-Intensity |
|---|---|---|---|
| **Reduction % in LDL-C** | **> 50% reduction of LDL with daily statin** | 30-50% reduction of LDL with daily statin | <30% reduction of LDL with daily statin |
| **Statin and dose** | **Atorvastatin *(40)*-80 mg**<br>**Rosuvastatin 20 *(40)* mg** | Atorvastatin 10 *(20)* mg<br>Rosuvastatin *(5)* 10 mg<br>Simvastatin 20-40 mg<br>Pravastatin 40 *(80)* mg<br>Lovastatin 40 mg<br>*Fluvastatin XL 80 mg*<br>Fluvastatin 40 mg bid<br>***Pitavastatin 2-4 mg*** | *Simvastatin 10 mg*<br>Pravastatin 10-20 mg<br>Lovastatin 20 mg<br>*Fluvastatin 20-40 mg*<br>*Pitavastatin 1 mg* |

* Specific statins and doses are noted in bold that were evaluated in RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA ***but were not tested in the RCTs reviewed are listed in italics***.

Stone NJ, et al Circulation 2013

## Intensity of Statin and LDL-c reduction in Korean

**Table 2.** Comparison in response to rosuvastatin or atorvastatin between Asian and Westerner

| | Rosuvastatin | | | Atorvastatin | | |
|---|---|---|---|---|---|---|
| | Asian (N=304) | Westerner (N=869) | *P* | Asian (N=366) | Westerner (N=772) | *P* |
| LDL-C at baseline | 123.1±14.6 | 124.2±5.1 | 0.93 | 124.1±12.7 | 129.8±14.2 | 0.61 |
| LDL-C at follow-up | 67.2±13.8 | 61.9±0.9 | 0.64 | 72.9±14.2 | 73.1±4.1 | 0.97 |
| LDL-C reduction (%) | 44.0±4.8 | 49.9±2.6 | 0.22 | 40.7±5.5 | 43.0±2.1 | 0.60 |
| Statin dose (mg) | 14.1±4.9 | 40.0±0.0 | 0.006 | 18.9±2.9 | 80.0±0.0 | <0.001 |
| Duration (month) | 10.3±3.7 | 24.0±0.0 | 0.016 | 7.8±2.2 | 22.0±2.8 | <0.001 |

Naito R et al. J Atheroscler Thromb. 2017

표 4-3. 현재 쓰이는 스타틴의 지질조절 유효성에 대한 한국인 자료

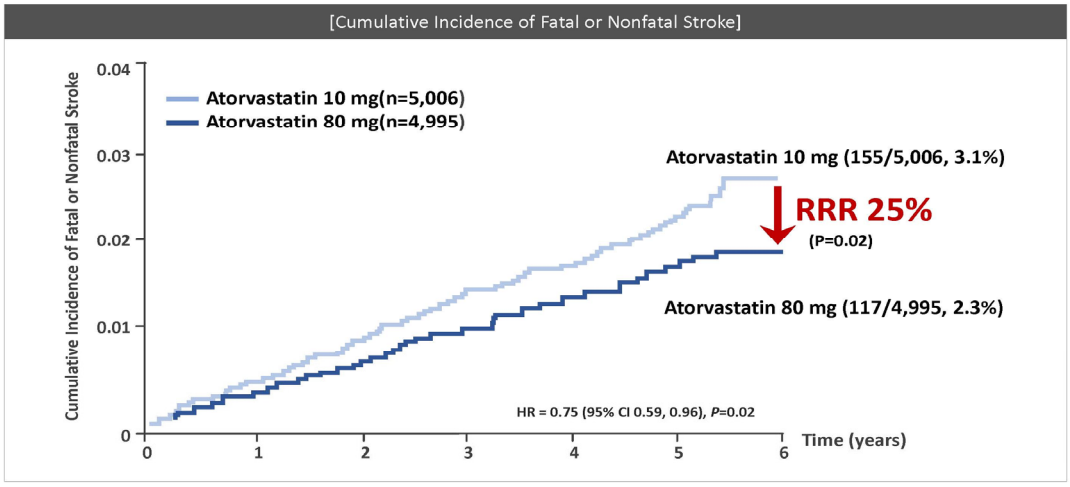
| | Lovastatin | Pravastatin | Simvastatin | Atorvastatin | Rosuvastatin | Pitavastatin |
|---|---|---|---|---|---|---|
| 하루 용량 (mg) | 20 | | | | | |
| 용량별 유효성 (%) | | | | | | |
| LDL-C | -32~-34 | | | | | |
| TG | -3~-29 | | | | | |
| HDL-C | -2~15 | | | | | |
| 하루 용량 (mg) | | 40 | 20 | 10 | 5 | 2 |
| 용량별 유효성 (%) | | | | | | |
| LDL-C | | -28~-33 | -27~-39 | -39~-44 | -40~-49 | -38~-44 |
| TG | | -13~-15 | -7~-14 | -2~-19 | -7~-23 | -13~-14 |
| HDL-C | | 0 | 6-12 | 3-6 | 4~7 | 5~16 |
| 하루 용량 (mg) | | | | 20 | 10 | |
| 용량별 유효성 (%) | | | | | | |
| LDL-C | | | | -41~-50 | -42~-50 | |
| TG | | | | -4~-33 | -12~-32 | |
| HDL-C | | | | -1~-19 | -10~20 | |
| 하루 용량 (mg) | | | | 40 | 20 | |
| 용량별 유효성 (%) | | | | | | |
| LDL-C | | | | -52~-59 | -50~-60 | |
| TG | | | | -21~-22 | -25 | |
| HDL-C | | | | -5 | -1 | |
| 하루 용량 (mg) | | | | 80 | | |
| 용량별 유효성 (%) | | | | | | |
| LDL-C | | | | -56 | | |
| TG | | | | -17 | | |
| HDL-C | | | | 자료없음 | | |

## High dose statin and beyond LDL lowering effect

## MORE INTENSIVE Statins?

**TNT**

**10,001 patients with CHD randomized Atorvastatin 10 mg or 80 mg**




*TNT = Treating to New Targets; RRR = relative risk reduction.

LaRosa JC, et al. N Engl J Med 2005;352:1425-1435

## Effect on ISCHEMIC stroke by MORE INTENSIVE Statins

**Meta-analysis 2010**

| Comparison & trial | LDL–C reduction (mmol/L) | Events (% p.a.) Statin/more | Events (% p.a.) Control/less | RR (CI) per 1 mmol/L reduction in LDL–C |
|---|---|---|---|---|
| **More vs. less statin** | | | | |
| PROVE-IT | 0.65 | 10 (0.2) | 12 (0.3) | |
| TNT | 0.62 | 96 (0.4) | 130 (0.5) | |
| IDEAL | 0.55 | 129 (0.6) | 158 (0.8) | |
| SEARCH | 0.39 | 183 (0.5) | 195 (0.5) | |
| A to Z | 0.30 | 22 (0.6) | 31 (0.8) | |
| **Subtotal (5 trials)** | **0.51** | **440/19829 (0.5% p.a.)** | **526/19783 (0.6% p.a.)** | **0.69 (0.54 – 0.88) p=0.003** |

Trend: $\chi^2_1 = 0.3$ (p=0.6)

0.5 0.75 1 1.25 1.5

Statin better Control better

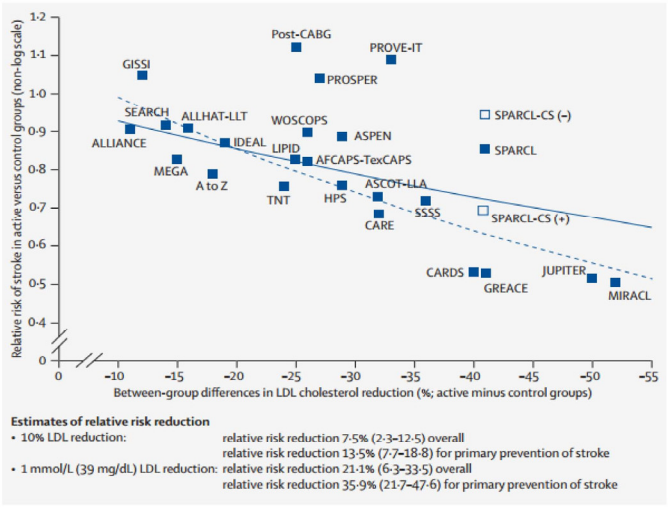
**LDL –C 1 mmol/L (39mg/dL) ↓, RR 31%**

CTT Collaboration, et al. Lancet 2010;376:1670-1681

## Lowering LDL with Statins Reduces the Risk of Stroke

**Meta-analysis of 24 trials with 165,792 patients**

[Association between reduction in LDL cholesterol concentration with stroke incidence]



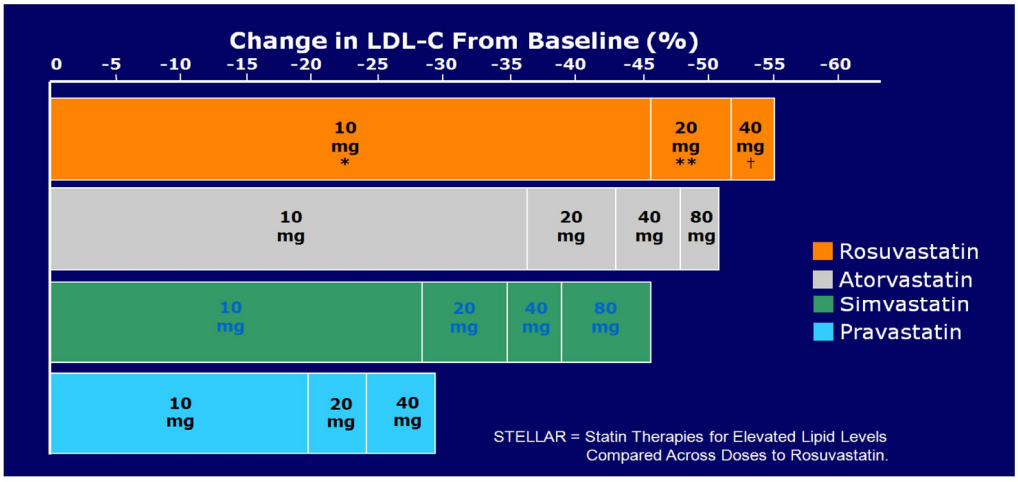

**Estimates of relative risk reduction**

- 10% LDL reduction: relative risk reduction 7·5% (2·3–12·5) overall; relative risk reduction 13·5% (7·7–18·8) for primary prevention of stroke
- 1 mmol/L (39 mg/dL) LDL reduction: relative risk reduction 21·1% (6·3–33·5) overall; relative risk reduction 35·9% (21·7–47·6) for primary prevention of stroke

**LDL–C 39mg/dL ↓,**
**Risk for overall stroke**
**21.1% ↓ (p<0.009)**

Amarenco P, et al. Lancet Neurol. 2009;8(5):453-63

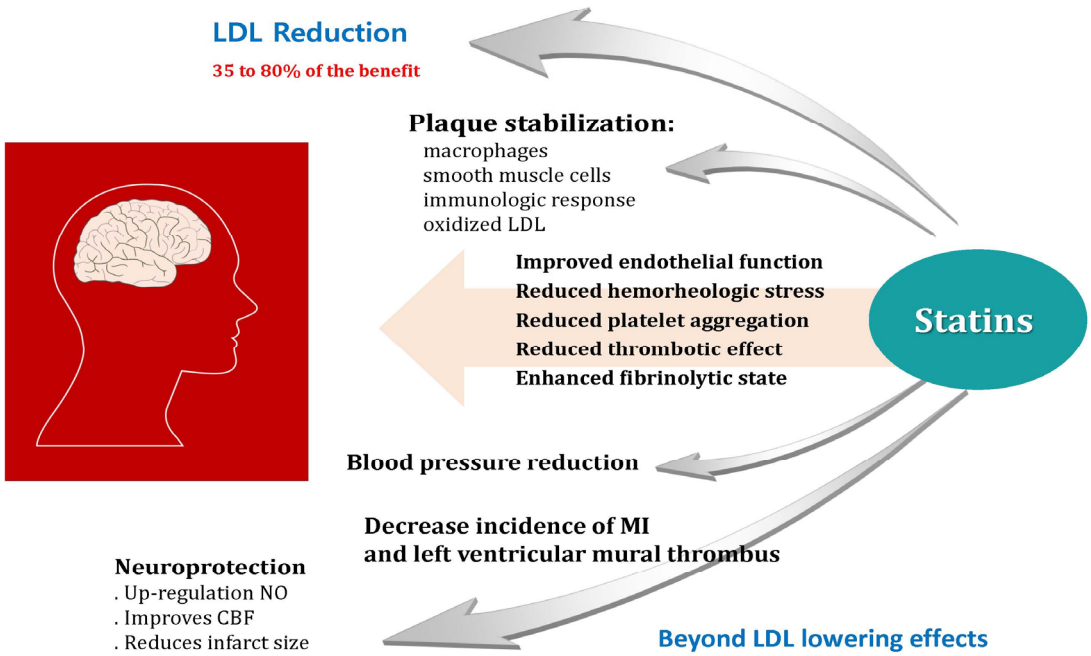
## Percentage Change in LDL-C: Pairwise Comparisons




*$P$<.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg.
**$P$<.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg.
†$P$<.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg.

Jones et al. Am J Cardiol 2003;92:152–160

## Potential Statin Mechanisms of Benefit




## Effect of statin pretreatment in carotid artery stenting

### Dose-Dependent Effect of Statin Pretreatment on Preventing the Periprocedural Complications of Carotid Artery Stenting

Jeong-Ho Hong, MD; Sung-Il Sohn, MD; Jaehyuk Kwak, MD; Joonsang Yoo, MD; Hyuk Won Chang, MD; O-Ki Kwon, MD; Cheolkyu Jung, MD; Inyoung Chung, MD; Hee-Joon Bae, MD; Ji Sung Lee, PhD; Moon-Ku Han, MD

***Background and Purpose***—We investigated whether statin pretreatment can dose dependently reduce periprocedural complications in patients undergoing carotid artery stenting because of symptomatic carotid artery stenosis.

***Methods***—We enrolled a consecutive series of 397 symptomatic carotid artery stenosis (≥50% stenosis on conventional angiography) treated with carotid artery stenting at 2 tertiary university hospitals over a decade. Definition of periprocedural complications included any stroke, myocardial infarction, and death within 1 month after or during the procedure. Statin pretreatment was divided into 3 categories according to the atorvastatin equivalent dose: none (n=158; 39.8%), standard dose (<40 mg of atorvastatin, n=155; 39.0%), and high dose (≥40 mg; n=84; 21.2%). A multivariable logistic regression analysis with the generalized estimating equation method was used to investigate independent factors in periprocedural complications.

***Results***—The patients' mean age was 68.7 years (81.6% men). The periprocedural complication rates across the 3 categories of statin use were 12.0%, 4.5%, and 1.2%. After adjustment, a change in the atorvastatin dose category was associated with reduction in the odds of periprocedural complications for each change in dose category (standard-dose statin: odds ratio, 0.24; 95% confidence interval, 0.07–0.81; high-dose statin: odds ratio, 0.11; 95% confidence interval, 0.01–0.96; *P* for trend=0.01). Administration of antiplatelet drugs was also an independent factor in periprocedural complications (OR, 0.18; 95% CI, 0.05–0.69).

***Conclusions***—This study shows that statin pretreatment may reduce the incidence of periprocedural complications dose dependently in patients with symptomatic carotid artery stenting. (***Stroke*. 2017;48:1890-1894. DOI: 10.1161/STROKEAHA.117.016680.**)

# High dose statin and beyond LDL lowering effect

**Table 2. Periprocedural Complications Within 30 Days After Stenting for Symptomatic Carotid Artery Stenosis**

| | Total (n=397) | No Statin (n=158) | Standard-Dose Statin (n=155) | High-Dose Statin (n=84) | *P* Value |
|---|---|---|---|---|---|
| Periprocedural complications, n (%) | 27 (6.8) | 19 (12.0) | 7 (4.5) | 1 (1.2) | 0.002 |
| Immediate procedural events | 16 (4.0) | 11 (7.0) | 5 (3.2) | 0 (0) | 0.026 |
| Ischemic stroke | 8 (2.0) | 5 (3.2) | 3 (1.9) | 0 (0) | |
| Hemorrhagic stroke | 6 (1.5) | 4 (2.5) | 2 (1.3) | 0 (0) | |
| Myocardial infarction | 1 (0.3) | 1 (0.6) | 0 (0) | 0 (0) | |
| Death | 2 (0.5) | 2 (1.3) | 0 (0) | 0 (0) | |
| 30-d clinical events | 14 (3.5) | 10 (6.3) | 3 (1.9) | 1 (1.2) | 0.046 |
| Ischemic stroke | 4 (1.0) | 4 (2.5) | 0 (0) | 0 (0) | |
| Hemorrhagic stroke | 1 (0.3) | 0 (0) | 0 (0) | 1 (1.2) | |
| Myocardial infarction | 3 (0.8) | 1 (0.6) | 2 (1.3) | 0 (0) | |
| Death | 7 (1.8) | 6 (3.8) | 1 (0.6) | 0 (0) | |

**Table 4. Lipid Profiles Stratified According to Statin Dose**

| | Total (92.5%; 347/375) | No Statin (89.5%; 136/152) | Standard-Dose Statin (92.5%; 135/146) | High-Dose Statin (98.7%; 76/77) | *P* Value |
|---|---|---|---|---|---|
| Total cholesterol | 174.0±43.7 | 171.9±37.9 | 179.5±50.6 | 167.9±39.5 | 0.14 |
| Triglyceride | 132.9±76.1 | 133.5±76.9 | 138.6±84.4 | 121.7±56.6 | 0.3 |
| HDL | 42.1±10.6 | 42.5±11.3 | 42.2±9.7 | 41.5±11.0 | 0.8 |
| LDL | 103.1±35.6 | 100.4±29.2 | 108.5±42.0 | 98.4±32.8 | 0.07 |

Data are shown for subjects with a complete lipid profile. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

# Effects of statin in symptomatic intracranial atherosclerosis

**Plaque enhancement**

- Symptomatic plaque
- Neovascularization,
- Increased endothelial permeability

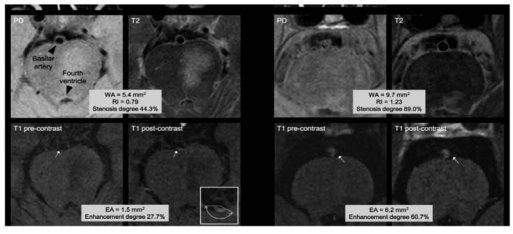
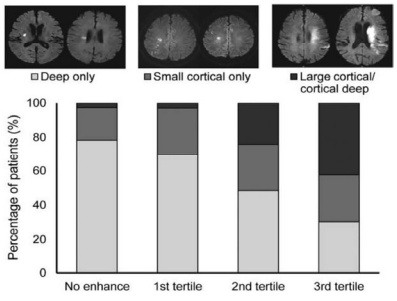



**Table 3. Multivariable Analysis: Coefficients for Associations Between Patient Characteristics and the Enhancement Volume of Symptomatic Intracranial Plaque**

| | Univariate Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| | Coefficient | SE | *P* Value | Coefficient | SE | *P* Value |
| Age | −0.89 | 1.23 | 0.427 | | | |
| Male sex | 9.44 | 6.40 | 0.143 | | | |
| Body mass index, kg/m² | 1.70 | 0.88 | 0.056 | 1.40 | 0.85 | 0.102 |
| Hypertension | −8.91 | 6.51 | 0.174 | | | |
| Diabetes mellitus | 3.41 | 6.92 | 0.623 | | | |
| Current smoking | 6.35 | 7.86 | 0.421 | | | |
| White blood cell, 10⁹/L | 2.63 | 1.24 | 0.035 | 1.83 | 1.22 | 0.137 |
| Fasting glucose, by 10-mg/dL increase | 0.02 | 1.30 | 0.989 | | | |
| hsCRP, mg/dL | 8.41 | 4.01 | 0.038 | 4.20 | 3.89 | 0.281 |
| ESR, mm/h | −0.02 | 0.19 | 0.907 | | | |
| Lp-PLA$_2$, mg/dL | 0.42 | 0.14 | 0.002 | 0.31 | 0.13 | 0.024 |
| Total cholesterol, mg/dL | 0.02 | 0.07 | 0.795 | | | |
| LDL cholesterol, mg/dL | 0.05 | 0.08 | 0.516 | | | |
| Premorbid statin use | | | | | | |
| Nonuser (reference) | | | | | | |
| Low-dose user | −20.12 | 8.38 | 0.018 | −16.61 | 8.27 | 0.047 |
| High-dose user | −30.13 | 9.58 | 0.002 | −29.78 | 9.44 | 0.002 |

ESR indicates erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$.




Stroke. 2015;46:2815-2821, Chung JW et al. Stroke. 2016;47:1789-96

# Statin in acute stroke phase

## Statin at stroke onset and stroke outcome

### Statin Therapy and Outcome After Ischemic Stroke
#### Systematic Review and Meta-Analysis of Observational Studies and Randomized Trials

**Table. Comparison of Statin at Stroke Onset and Fatality From Observational Studies With and Without Inclusion of Riks-Stroke Data (n=86 651)**

| | | Including Riks-Stroke (n=113 148) | | | Excluding Riks-Stroke (n=26 497) | | |
|---|---|---|---|---|---|---|---|
| | | n | OR (95% CI) | *P* Value | n | OR (95% CI) | *P* Value |
| Good functional outcome (mRS 0–2) | 30 days/ discharge | 17 512 | 1.64 (1.14–2.36) | 0.008 | 17 512 | 1.64 (1.14–2.36) | 0.008 |
| | 90 days | 17 606 | 1.41 (1.29–1.56) | <0.001 | 3077 | 1.32 (1.08–1.61) | 0.007 |
| | 1 yr | 2306 | 1.12 (0.90–1.40) | 0.31 | 2306 | 1.12 (0.90–1.40) | 0.31 |
| Fatality | 30 days/ discharge | 109 837 | 0.63 (0.54–0.74) | <0.001 | 23 186 | 0.61 (0.49–0.78) | <0.001 |
| | 90 days | 101 615 | 0.71 (0.62–0.82) | <0.001 | 14 964 | 0.82 (0.74–0.91) | <0.001 |
| | 1 yr | 101 664 | 0.80 (0.67–0.95) | 0.01 | 15 013 | 0.90 (0.66–1.24) | 0.53 |

Stroke. 2013;44:448-456

## Pre-stroke statin effect in acute stroke phase

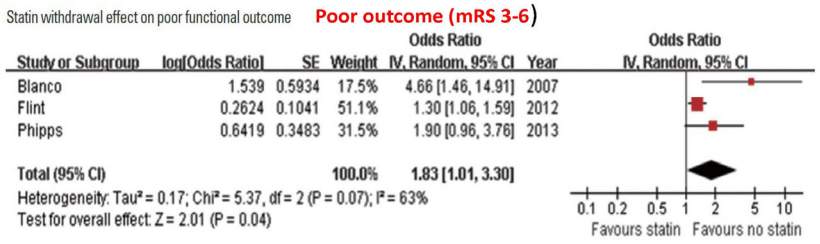
- Milder initial stroke severity (lower NIHSS) at stroke onset
- Smaller infarct volume
- Better functional outcome (at discharge and at 3 months)
- Lower short-term mortality

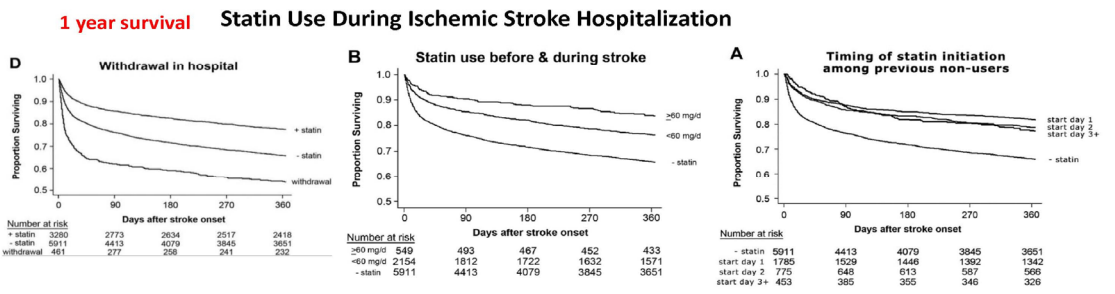
**Treatment with IV thrombolysis**

- Higher collateral grade after cerebral artery occlusion
- Greater reperfusion and NIHSS improvement
- Increased hemorrhagic transformation (?)
  - antithrombotic effect, faciliating fibrinoysis
- Lower mortality (?)

Neurology 2007;682129-31
Neurology 2011;77:888–895
Neurology 2006;67:1403–1410
Neurology 2013;80:1800–1805
Journal of Stroke 2015;17(3):282-301

## Statin withdrawl after ischemic stroke



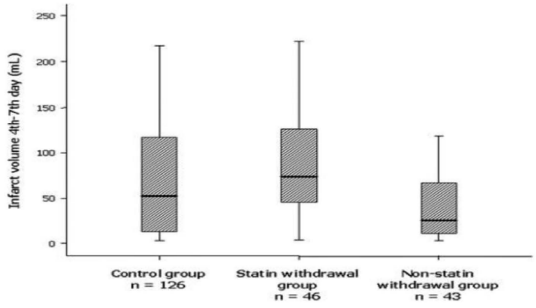

Journal of Stroke 2015;17(3):282-301
Stroke 2011;42:1307-1313

## Statin withdrawl after ischemic stroke (RCT)

- Patients on chronic statin Tx within 24 hrs
- Statin withdrawal for 3 days vs. atorvastatin 20 mg

Table 2 Unadjusted and adjusted ORs of death or dependency and END in patients with and without statin withdrawal

| | Statin-withdrawal group, n (%) | Non-statin-withdrawal group, n (%) | OR (95% CI) | Adjusted OR (95% CI)* |
|---|---|---|---|---|
| Primary outcome event† | 27 (60.0) | 16 (39.0) | 2.39 (1.02, 5.62) | 4.66 (1.46, 14.91) |
| Early neurologic deterioration | 30 (65.2) | 9 (20.9) | 7.08 (2.73, 18.37) | 8.67 (3.05, 24.63) |



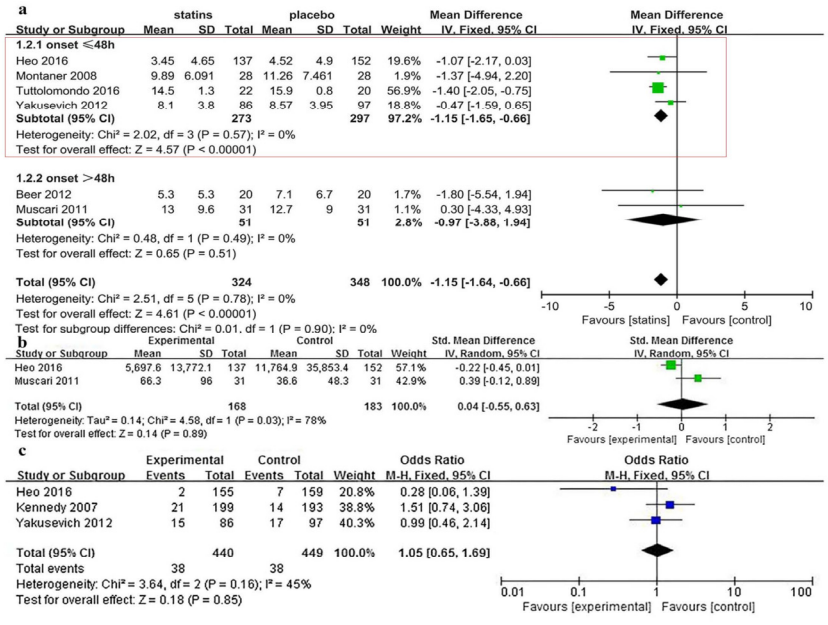

Neurology 2007;69:904–910

## Efficacy of high dose statin in acute stroke phase (RCTs)

A. NIHSS score

B. Infarct volume

C. Recurrence of stroke.

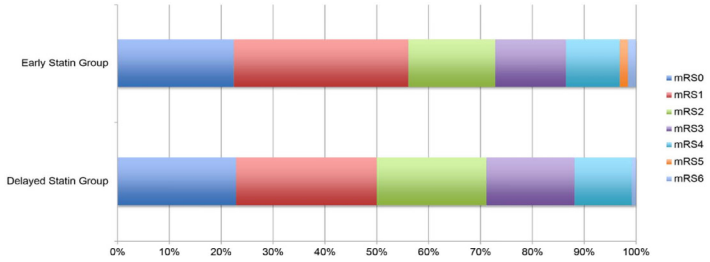



Fang et al. Intern Emerg Med 2017

## Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke

### ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient)

- 24 hrs after admission in the early group vs on the seventh day in the delayed group
- Aatorvastatin 20 mg/d, pitavastatin 4 mg/d, or rosuvastatin 5 mg/d
- LDL-C < 70 mg/dL for both groups

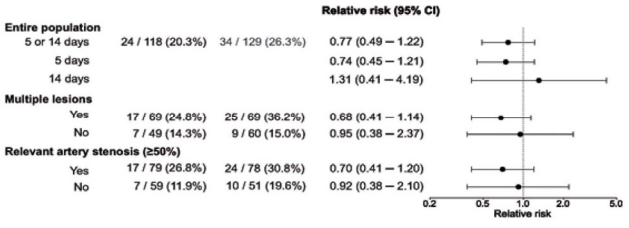



| | mRS at 90 days | 0 | 1 | 2 | 3 | 4 | 5 | 6 | p-value |
|---|---|---|---|---|---|---|---|---|---|
| Early Statin Group (n=125) | n (%) | 28 (21.4) | 42 (32.1) | 21 (16.0) | 17 (13.0) | 13 (9.9) | 2 (1.5) | 2 (1.5) | 0.70 |
| Delayed Statin Group (n=118) | n (%) | 27 (21.4) | 32 (25.4) | 25 (19.8) | 20 (15.9) | 13 (10.3) | 0 (0.0) | 1 (0.8) | |

Yoshimura et al. *Stroke* 2017

## Efficacy of high-dose statin in acute stroke phase

- Patients with DWI within 48 hours after symptom onset.
- Rosuvastatin 20 mg vs placebo
- The primary outcome was occurrence of new ischemic lesions on DWI at 5 or 14 days.




Occurrence of intracranial hemorrhagic transformation on gradient-recalled echo (GRE)

| | Rosuvastatin (n = 137) | Placebo (n = 152) | *P* value |
|---|---|---|---|
| HI1 | 2 (1.4) | 15 (9.9) | 0.002 |
| HI2 | 2* (1.4) | 7† (4.6) | 0.177 |
| PH1 | 1 (0.7) | 0 (0.0) | 0.478 |
| PH2 | 0 (0.0) | 0 (0.0) | |
| Radiological subarachnoid hemorrhage | 1 (0.7) | 0 (0.0) | 0.478 |
| Any hemorrhagic transformation | 6 (4.3) | 22 (14.5) | 0.007 |

The efficacy of rosuvastatin in reducing recurrence in acute stroke was inconclusive. However, statin use was safe and reduced hemorrhagic transformation.

Heo JH et al. J Stroke. 2016 ; 18: 87–95

## Guidelines for the Early Management of AIS

### 2018 AHA/ASA Guidelines

1. Among patients already taking statins at the time of onset of ischemic stroke, **continuation of statin therapy during the acute period** is reasonable. *(Class IIa; Level of Evidence B-R).*

2. **High-intensity statin therapy should be initiated or continued** as first-line therapy in women and men ≤75 years of age who have clinical ASCVD*, unless contraindicated.*(Class I ; Level of Evidence A).*

3. In individuals with clinical ASCVD* in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, **moderate-intensity statin** should be used as the second option if tolerated. (Class I ;Level of Evidence A).

4. In individuals with clinical ASCVD>75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.(Class IIb ; Level of Evidence B-R).

Powers WJ et al. Stroke. 2018

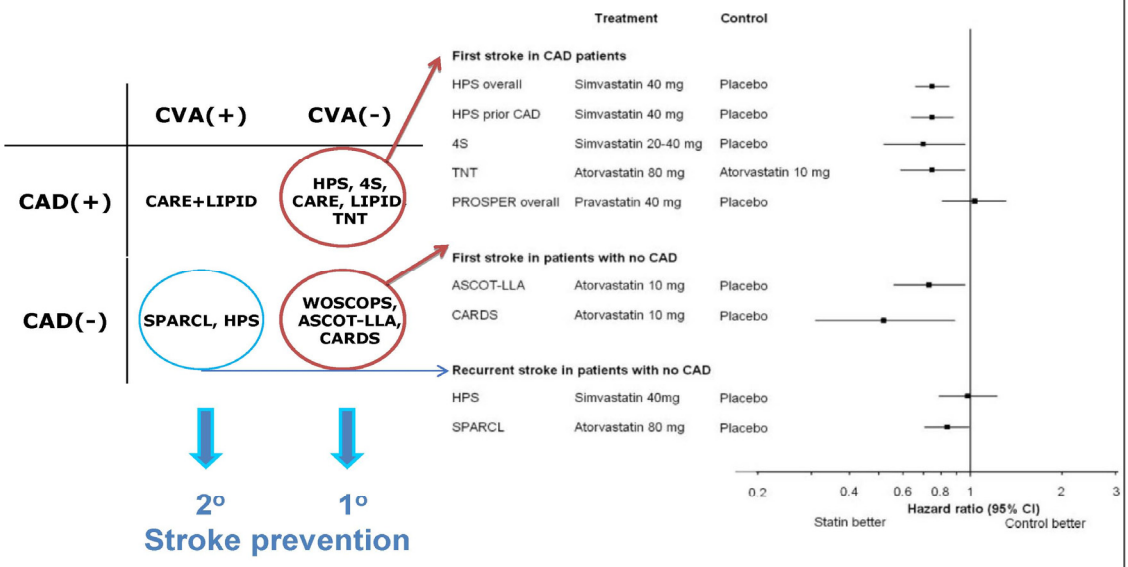
### Recommendations from the ESO-Karolinska Stroke Update

1. There is no evidence from RCTs to support the routine use of statins in the acute phase of stroke (first 2 weeks). However, observational studies do not show an increase in symptomatic ICH in patients previously treated with statins or to whom statin was given within 3 days after stroke. **Statin treatment is thus recommended** to start before discharge from hospital after an AIS or at least during follow-up (Grade C).

Euro Stroke J 2017

## Statin for secondary stroke prevention

## Stroke Prevention by Statin

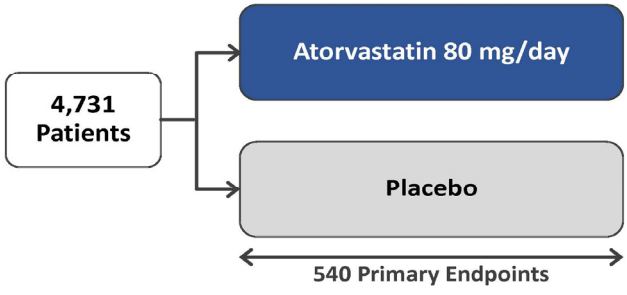



## The First & only evidence for secondary prevention

### SPARCL study

**Patient Population**

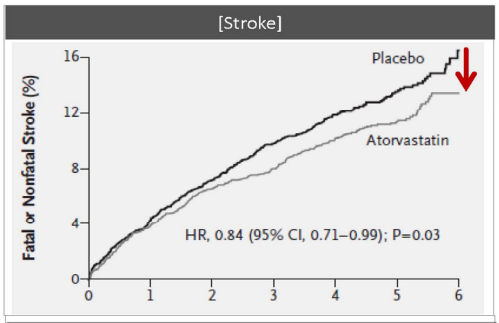
- 205 sites worldwide
- Previously documented stroke or TIA within 6 months
- No history of CHD
- LDL-C levels ≥100 mg/dL and ≤190 mg/dL




**Primary End Point**
**Time to the First Occurrence of a Fatal or Nonfatal Stroke**

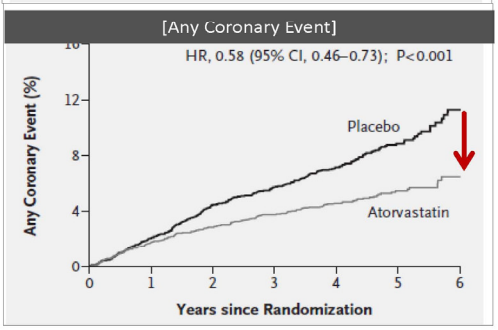
SPARCL Investigators, et al. N Engl J Med 2006;355:549-59

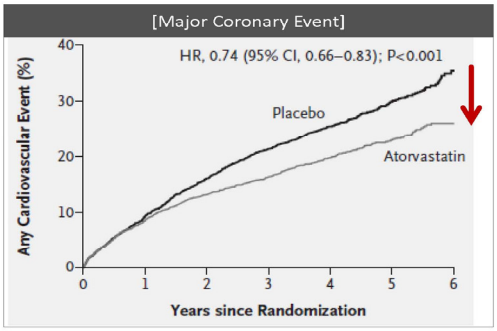
## Benefit of Atorvastatin 80 mg in Patient with Prior Stroke




**SPARCL study**

- ✓Risk for Recurrence Stroke 16%↓
- ✓Risk for Any Coronary Event 42%↓
- ✓Risk for Major Coronary Event 26%↓




SPARCL Investigators, et al. N Engl J Med 2006;355:549-59

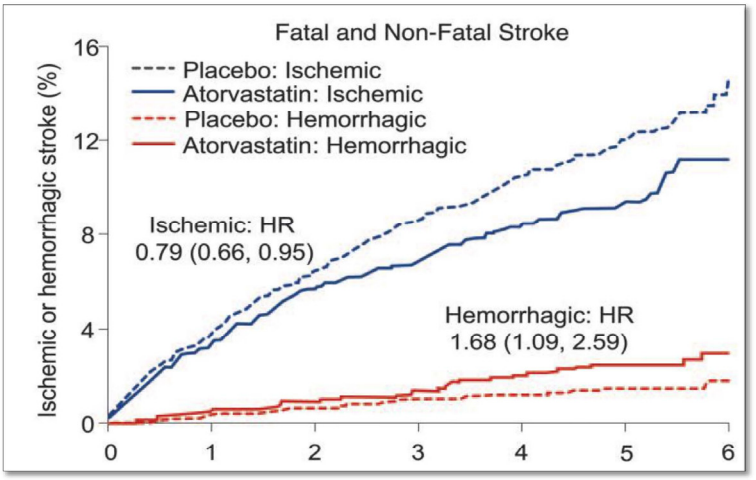
## Safety of Atorvastatin 80 mg in Patient with Prior Stroke

[Liver and Muscle Adverse Events]

| | Atorvastatin n/N(%) | Placebo n/N(%) |
|---|---|---|
| ALT or AST >3x ULN* | 51/2319 (2.2) | 11/2323 (0.4) |
| CPK >10x ULN* | 2/2319 (0.1) | 0/2319 (0.0) |
| Musculoskeletal Adverse Events | | |
| Myalgia | 129/2365 (5.5) | 141/2366 (6.0) |
| Myopathy | 7/2365 (0.3) | 7/2366 (0.3) |
| Rhabdomyolysis | 2/2365 (0.1) | 3/2366 (0.1) |

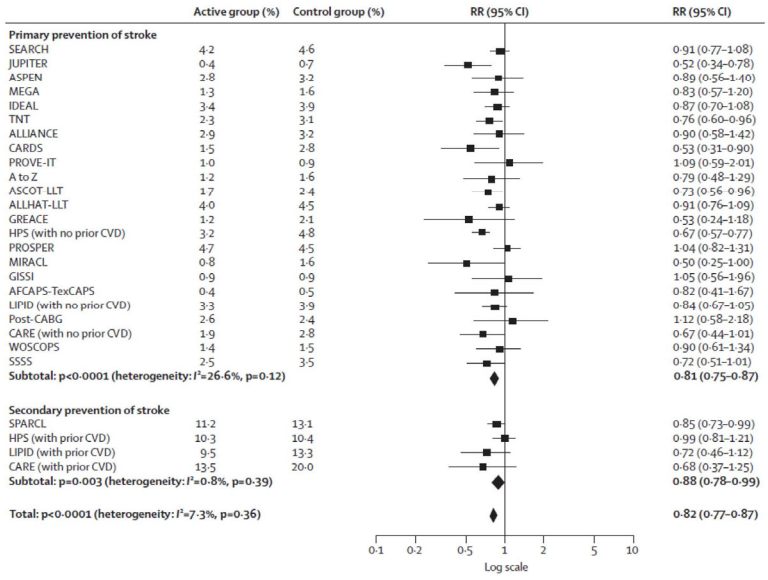
SPARCL Investigators, et al. N Engl J Med 2006;355:549-59

## Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study



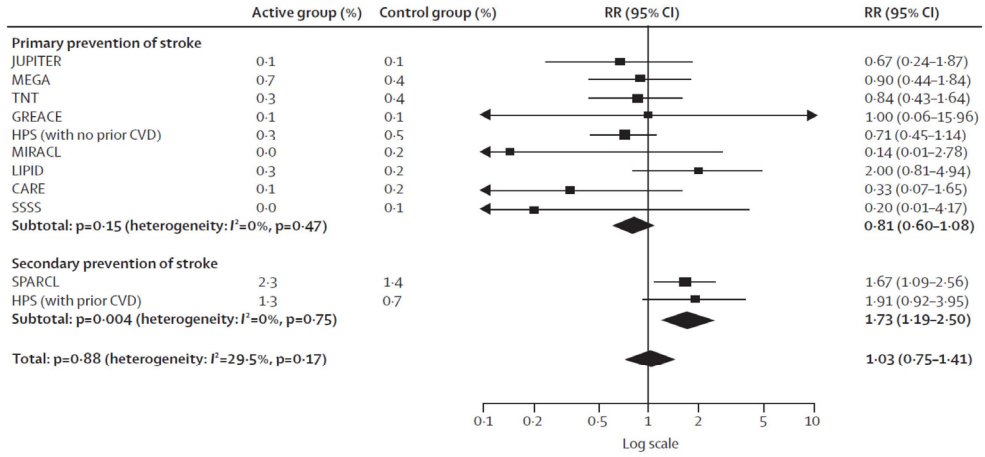

Neurology 2008;70:2364-2370

## Effect of statins on fatal and non-fatal stroke



| | Active group (%) | Control group (%) | RR (95% CI) |
|---|---|---|---|
| **Primary prevention of stroke** | | | |
| SEARCH | 4·2 | 4·6 | 0·91 (0·77–1·08) |
| JUPITER | 0·4 | 0·7 | 0·52 (0·34–0·78) |
| ASPEN | 2·8 | 3·2 | 0·89 (0·56–1·40) |
| MEGA | 1·3 | 1·6 | 0·83 (0·57–1·20) |
| IDEAL | 3·4 | 3·9 | 0·87 (0·70–1·08) |
| TNT | 2·3 | 3·1 | 0·76 (0·60–0·96) |
| ALLIANCE | 2·9 | 3·2 | 0·90 (0·58–1·42) |
| CARDS | 1·5 | 2·8 | 0·53 (0·31–0·90) |
| PROVE-IT | 1·0 | 0·9 | 1·09 (0·59–2·01) |
| A to Z | 1·2 | 1·6 | 0·79 (0·48–1·29) |
| ASCOT LLT | 1·7 | 2·4 | 0·73 (0·56–0·96) |
| ALLHAT-LLT | 4·0 | 4·5 | 0·91 (0·76–1·09) |
| GREACE | 1·2 | 2·1 | 0·53 (0·24–1·18) |
| HPS (with no prior CVD) | 3·2 | 4·8 | 0·67 (0·57–0·77) |
| PROSPER | 4·7 | 4·5 | 1·04 (0·82–1·31) |
| MIRACL | 0·8 | 1·6 | 0·50 (0·25–1·00) |
| GISSI | 0·9 | 0·9 | 1·05 (0·56–1·96) |
| AFCAPS-TexCAPS | 0·4 | 0·5 | 0·82 (0·41–1·67) |
| LIPID (with no prior CVD) | 3·3 | 3·9 | 0·84 (0·67–1·05) |
| Post-CABG | 2·6 | 2·4 | 1·12 (0·58–2·18) |
| CARE (with no prior CVD) | 1·9 | 2·8 | 0·67 (0·44–1·01) |
| WOSCOPS | 1·4 | 1·5 | 0·90 (0·61–1·34) |
| 5SSS | 2·5 | 3·5 | 0·72 (0·51–1·01) |
| **Subtotal: p<0·0001 (heterogeneity: $I^2$=26·6%, p=0·12)** | | | **0·81 (0·75–0·87)** |
| **Secondary prevention of stroke** | | | |
| SPARCL | 11·2 | 13·1 | 0·85 (0·73–0·99) |
| HPS (with prior CVD) | 10·3 | 10·4 | 0·99 (0·81–1·21) |
| LIPID (with prior CVD) | 9·5 | 13·3 | 0·72 (0·46–1·12) |
| CARE (with prior CVD) | 13·5 | 20·0 | 0·68 (0·37–1·25) |
| **Subtotal: p=0·003 (heterogeneity: $I^2$=0·8%, p=0·39)** | | | **0·88 (0·78–0·99)** |
| **Total: p<0·0001 (heterogeneity: $I^2$=7·3%, p=0·36)** | | | **0·82 (0·77–0·87)** |

## Effects of statin on hemorrhagic stroke




Lancet Neurol 2009; 8: 453–63

## Factors associated with risk of ICH

**Table 1** Outcome ischemic, hemorrhagic, and total strokes by entry event and treatment group

| | Ischemic stroke | | | Hemorrhagic stroke | | | Any stroke* | | |
|---|---|---|---|---|---|---|---|---|---|
| Entry event | Atorvastatin, n/N (%) | Placebo, n/N (%) | HR (95% CI) | Atorvastatin, n/N (%) | Placebo, n/N (%) | HR (95% CI) | Atorvastatin, n/N (%) | Placebo, n/N (%) | HR (95% CI) |
| Large vessel atheroembolic or cardioembolic | 41/396 (10.4) | 64/401 (16.0) | 0.64 (0.43, 0.94) | 8/396 (2.0) | 7/401 (1.8) | 1.16 (0.42, 3.19) | 50/396 (12.6) | 72/401 (18.0) | 0.69 (0.48, 0.99) |
| TIA | 44/708 (6.2) | 55/752 (7.3) | 0.85 (0.57, 1.26) | 12/708 (1.7) | 12/752 (1.6) | 1.07 (0.48, 2.37) | 54/708 (7.6) | 66/752 (8.8) | 0.87 (0.60, 1.24) |
| Small vessel (lacunar) | 79/708 (11.2) | 102/701 (14.6) | 0.76 (0.57, 1.02) | 20/708 (2.8) | 4/701 (0.6) | 4.99 (1.71, 14.61) | 93/708 (13.1) | 109/701 (15.6) | 0.84 (0.64, 1.11) |
| Other or unknown cause* | 51/506 (10.1) | 51/463 (11.0) | 0.92 (0.62, 1.35) | 8/506 (1.6) | 8/463 (1.7) | 0.91 (0.34, 2.44) | 58/506 (11.5) | 60/463 (13.0) | 0.89 (0.62, 1.27) |
| Hemorrhagic stroke | 3/45 (6.7) | 2/48 (4.2) | 1.64 (0.27, 9.82) | 7/45 (15.6) | 2/48 (4.2) | 4.06 (0.84, 19.57) | 10/45 (22.2) | 4/48 (8.3) | 2.82 (0.89, 9.01) |
| All subjects | 218/2365 (9.2) | 274/2366 (11.6) | 0.79 (0.66, 0.95) | 55/2365 (2.3) | 33/2366 (1.4) | 1.68 (1.09, 2.59) | 265/2365 (11.2) | 311/2366 (13.1) | 0.85 (0.72, 1.00) |

| | Hazard ratio (95% CI) | *p* Value |
|---|---|---|
| Atorvastatin treatment | 1.69 (1.10, 2.60) | 0.02 |
| Male gender | 1.77 (1.11, 2.81) | 0.02 |
| Age, 10 y increment | 1.37 (1.12, 1.69) | 0.003 |
| Entry event = hemorrhagic stroke | 5.81 (2.91, 11.60) | <0.001 |
| Blood pressure | — | 0.01 |
| Normotension (SBP <120 and DBP <80 mm Hg)* | — | — |
| Pre-hypertension (SBP 120–139 or DBP 80–89 mm Hg) | 3.18 (0.76, 13.34) | 0.11 |
| Stage 1 hypertension (SBP 140–159 or DBP 90–99 mm Hg) | 3.49 (0.83, 14.61) | 0.09 |
| Stage 2 hypertension (SBP ≥160 or ≥100 mm Hg) | 6.19 (1.47, 26.11) | 0.01 |

| | Hazard ratio (95% CI) | *p* Value |
|---|---|---|
| Male gender | 2.21 (1.20, 4.09) | 0.01 |
| Age, 10 y increment | 1.40 (1.08, 1.81) | 0.01 |
| Entry event = hemorrhagic stroke | 8.38 (3.78, 18.56) | <0.001 |
| LDL cholesterol (quartiles, atorvastatin group) | — | 0.77 |
| LDL cholesterol <52 mg/dL (1st quartile, 12 events)* | — | — |
| LDL cholesterol 52 to 65 mg/dL (2nd quartile, 18 events) | 1.26 (0.60, 2.64) | 0.54 |
| LDL cholesterol 66 to 92 mg/dL (3rd quartile, 13 events) | 0.97 (0.44, 2.17) | 0.94 |
| LDL cholesterol ≥93 mg/dL (4th quartile, 45 events) | 1.37 (0.63, 2.98) | 0.43 |

## CV benefits vs DM risks in high intensity statin therapy

- Crestor 20mg vs placebo in primary prevention from the JUPITER trial
- Major risk factors for diabetes at study entry
  - Metabolic syndrome
  - Impaired fasting glucose,
  - Body-mass index (BMI) 30 kg/m² or higher
  - Glycated haemoglobin A1c (HbA1c) greater than 6% at entry

| | No major diabetes risk factors (n=6095) | | | | | One or more major diabetes risk factors (n=11 508) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Rosuvastatin | Placebo | Δ | HR (95% CI) | p value | Rosuvastatin | Placebo | Δ | HR (95% CI) | p value |
| Primary endpoint | 44 (0·69) | 91 (1·45) | −47 | 0·48 (0·33–0·68) | 0·0001 | 96 (0·80) | 157 (1·31) | −61 | 0·61 (0·47–0·79) | 0·0001 |
| Primary endpoint, any death | 118 (1·85) | 174 (2·77) | −56 | 0·67 (0·53–0·85) | 0·0007 | 175 (1·46) | 262 (2·18) | −87 | 0·67 (0·55–0·81) | 0·0001 |
| Primary endpoint, VTE, any death | 122 (1·92) | 187 (2·99) | −65 | 0·64 (0·51–0·81) | 0·0001 | 196 (1·64) | 289 (2·41) | −93 | 0·68 (0·57–0·81) | 0·0001 |
| MI, stroke, any death | 99 (1·55) | 147 (2·33) | −48 | 0·67 (0·52–0·86) | 0·002 | 139 (1·15) | 202 (1·67) | −63 | 0·69 (0·56–0·86) | 0·0006 |
| Any death | 89 (1·32) | 113 (1·69) | −24 | 0·78 (0·59–1·03) | 0·08 | 109 (0·85) | 132 (1·02) | −23 | 0·83 (0·64–1·07) | 0·15 |
| Diabetes | 12 (0·18) | 12 (0·18) | 0 | 0·99 (0·45–2·21) | 0·99 | 258 (2·12) | 204 (1·65) | 54 | 1·28 (1·07–1·54) | 0·01 |

Data for rosuvastatin and placebo are absolute number of events (incidence rate per 100 person-years). The primary endpoint was a composite of non-fatal myocardial infarction, non-fatal stroke, unstable angina or revascularisation, and cardiovascular death. Analyses are limited to first events only. VTE=venous thromboembolism. MI=myocardial infarction. Δ=absolute difference in events between rosuvastatin and placebo.

*Table 2:* Absolute number of events, incidence rates, and hazard ratios (HRs) for cardiovascular endpoints, death, and diabetes in the JUPITER trial in participants with or without major diabetes risk factors, according to random allocation to rosuvastatin or placebo

Lancet 2012; 380: 565–71

## Lipid Guidelines for patients with Ischemic Stroke/ TIA

### 2014 AHA/ASA Guidelines

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

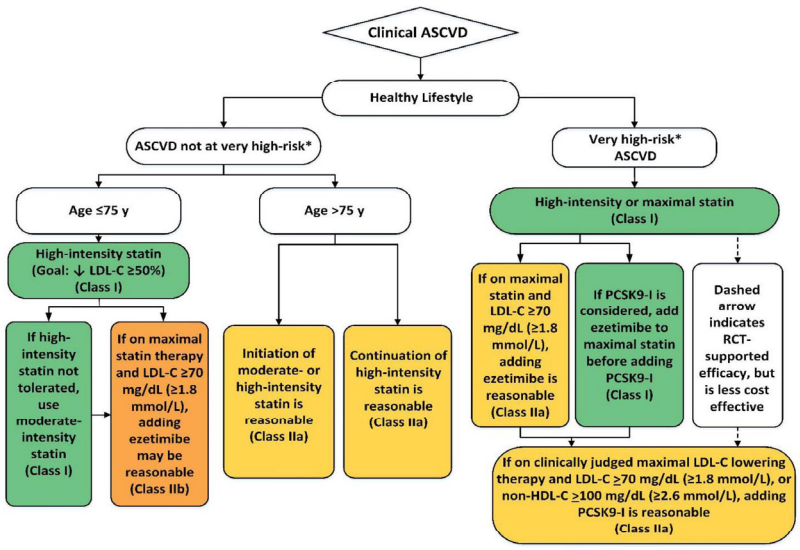
**Statin therapy with intensive lipid-lowering effects** is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, **an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD** *(Class I; Level of Evidence C)*

### Recommendations from the ESO-Karolinska Stroke Update

We recommend that **statins** be used as a part of standard secondary prophylactic treatment after an ischemic stroke or TIA. Benefits were **observed both with atorvastatin 80 mg and was simvastatin 40 mg** (Grade A). The use of statins in secondary prevention of ischemic stroke caused by less frequent non-atherosclerotic etiologies such as arterial dissection and PFO requires further investigations.

Euro Stroke J 2017

## 2018 American Lipid Guidelines for the Secondary Prevention




*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

## 2016 ESC/EAS Guidelines

**Table 4 Risk categories**

| | |
|---|---|
| **Very high-risk** | Subjects with any of the following:<br>• Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound.<br>• DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia.<br>• Severe CKD (GFR <30 mL/min/1.73 m²).<br>• A calculated SCORE ≥10% for 10-year risk of fatal CVD. |
| **High-risk** | Subjects with:<br>• Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.<br>• Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk).<br>• Moderate CKD (GFR 30–59 mL/min/1.73 m²).<br>• A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD. |
| **Moderate-risk** | SCORE is ≥1% and <5% for 10-year risk of fatal CVD. |
| **Low-risk** | SCORE <1% for 10-year risk of fatal CVD. |

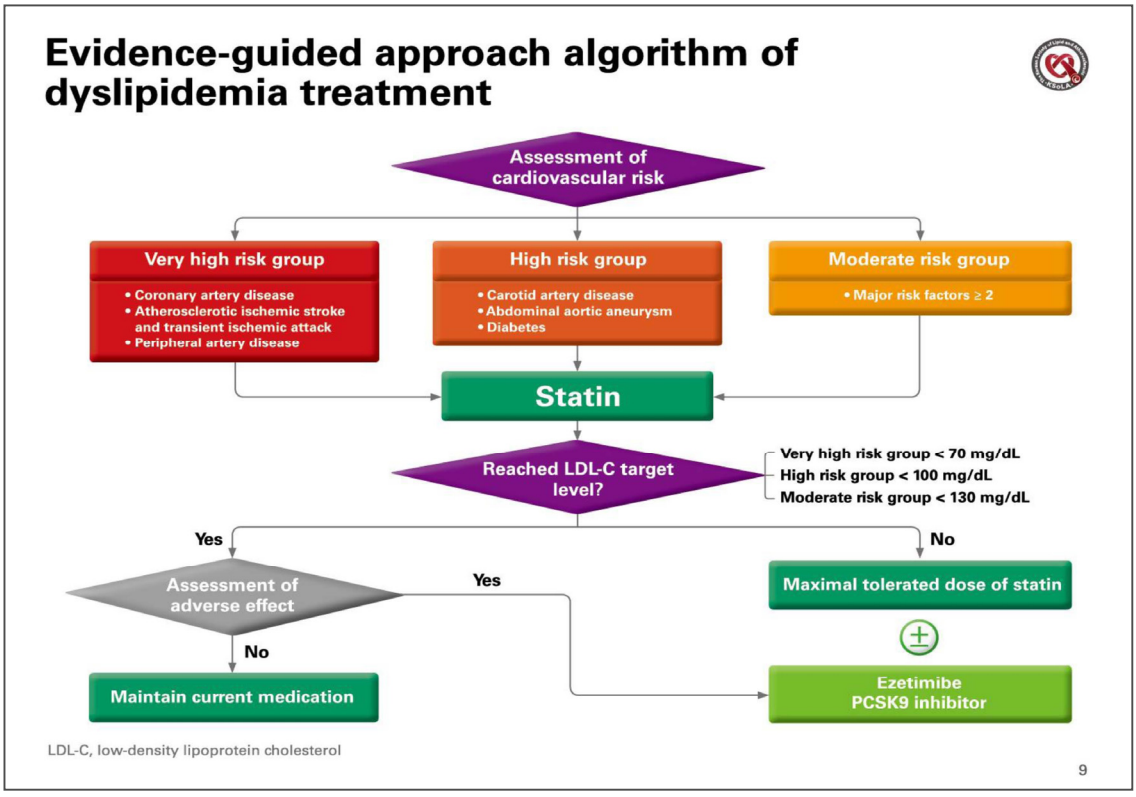
ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.

**Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol**

| Recommendations | Class [a] | Level [b] | Ref [c] |
|---|---|---|---|
| In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended. | I | B | 61, 62, 65, 68, 69, 128 |
| In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended. | I | B | 65, 129 |
| In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered. | IIa | C | - |

CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]For definitions see section 2.2.
[e]The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.

European Heart Journal 2016




# 이상지혈증 치료지침 및 국내 급여기준

표 2-3. 위험도 분류에 따른 LDL 콜레스테롤 및 non-HDL 콜레스테롤의 목표치

| 위험도 | LDL 콜레스테롤 목표 (mg/dL) | non-HDL 콜레스테롤 목표 (mg/dL) |
|---|---|---|
| 초고위험군<br>관상동맥질환<br>허혈성 뇌졸중<br>일과성 뇌허혈발작<br>말초혈관질환 | <70 | <100 |
| 고위험군<br>경동맥질환*<br>복부동맥류<br>당뇨병 | <100 | <130 |
| 중등도 위험군<br>주요위험인자 2개 이상 | <130 | <160 |
| 저위험군<br>주요위험인자 1개 이하 | <160 | <190 |

*50%가 넘는 경동맥 협착이 확인된 경우

표 2-4. LDL 콜레스테롤을 제외한 주요 위험인자*

| |
|---|
| 흡연 |
| 고혈압<br>수축기혈압 140 mmHg 이상 또는 이완기혈압 90 mmHg 이상<br>또는 항고혈압제 복용 |
| 저HDL 콜레스테롤(<40 mg/dL) |
| 연령<br>남자 45세 이상<br>여자 55세 이상 |
| 관상동맥질환 조기 발병의 가족력<br>부모, 형제자매 중 남자 55세 미만, 여자 65세 미만에서 관상동맥질환이 발병한 경우 |

*고HDL 콜레스테롤(60 mg/dL 이상)은 보호인자로 간주하여 총 위험인자 수에서 하나를 감하게 된다.

| 위험요인*에 따른 LCL-C 급여기준 | |
|---|---|
| 위험요인*이 0~1개인 경우 | LDL-C ≥ 160mg/dL |
| 위험요인*이 2개 이상인 경우 | LDL-C ≥ 130mg/dL |
| 관상동맥질환(CAD)이나 이에 준하는 위험인 경우 (말초동맥질환, 복부대동맥류, 증상이 동반된 경동맥 질환, 당뇨병 ) | LDL-C ≥ 100mg/dL |
| 급성관동맥증후군(ACS) | LDL-C ≥ 70mg/dL |

*위험요인

1.흡연 2.고혈압(≥140/90 mmHg) 또는 항고혈압제 복용 3.낮은 HDL-C*(<40mg/dL)
4.관상동맥질환 조기발병의 가족력** 5.나이(남자 45세,여자 55세)

* HDL-C≥60mg/dL은 보호인자로 간주하여 총 위험요인 수에서 하나를 감한다
** 부모 형제 자매 중 55세 미만 남자 65세 미만 여자에서 관상동맥질환이 발병한 경우

1. 보건복지부 고시 제2014-34호 (시행일:2014.03.01) 2. 보건복지부 고시 제2016-66호(시행일:2016.05.01)

## SUMMARY

- It is recommend statin therapy for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for CV events as recommended in the 2018 “ACC/AHA Guideline.
- Even though no evidence of large RCT, continuation and initiation of statin therapy during the acute period is reasonable.
- Intensive statin therapy is recommended to reduce risk of stroke and CV events among patients with atherosclerotic ischemic stroke or TIA.