# Στατίνες και καρδιαγγειακή πρόληψη

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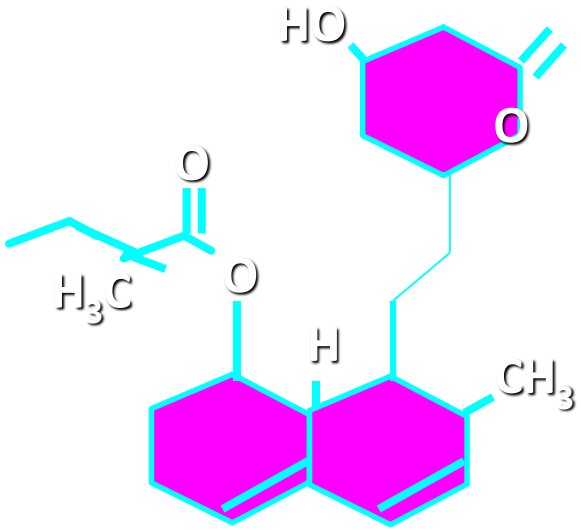
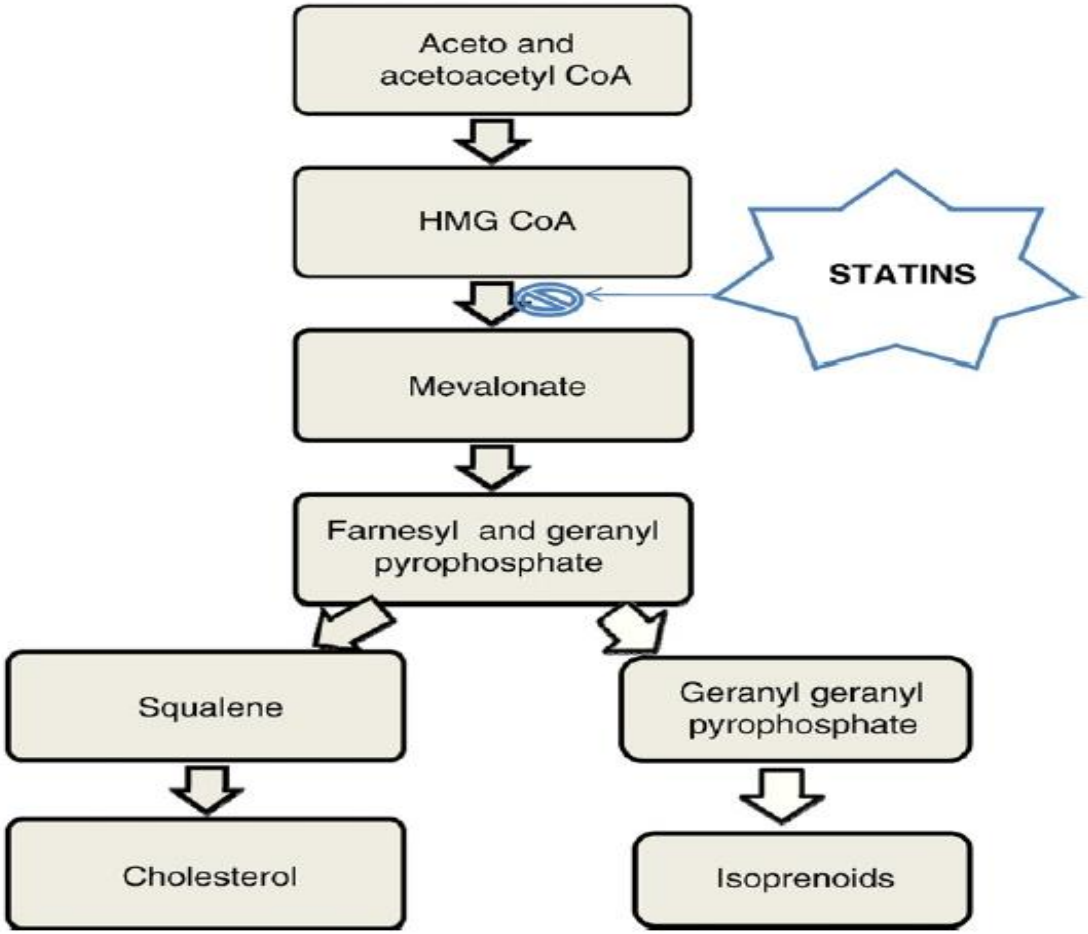
Akira
Endo



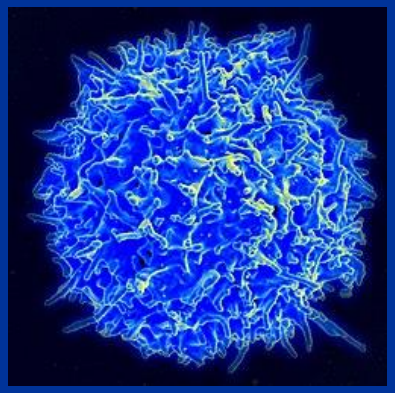

# How it works statins ……..



# Οι στατίνες…

↓ κυτοκίνες
IL-1B
IL-6
IL-8
IL-12
TNF

↓ δραστηριότητα
T-cells



↓χυμοκίνες
MCP1
RANTES

↓ CRP

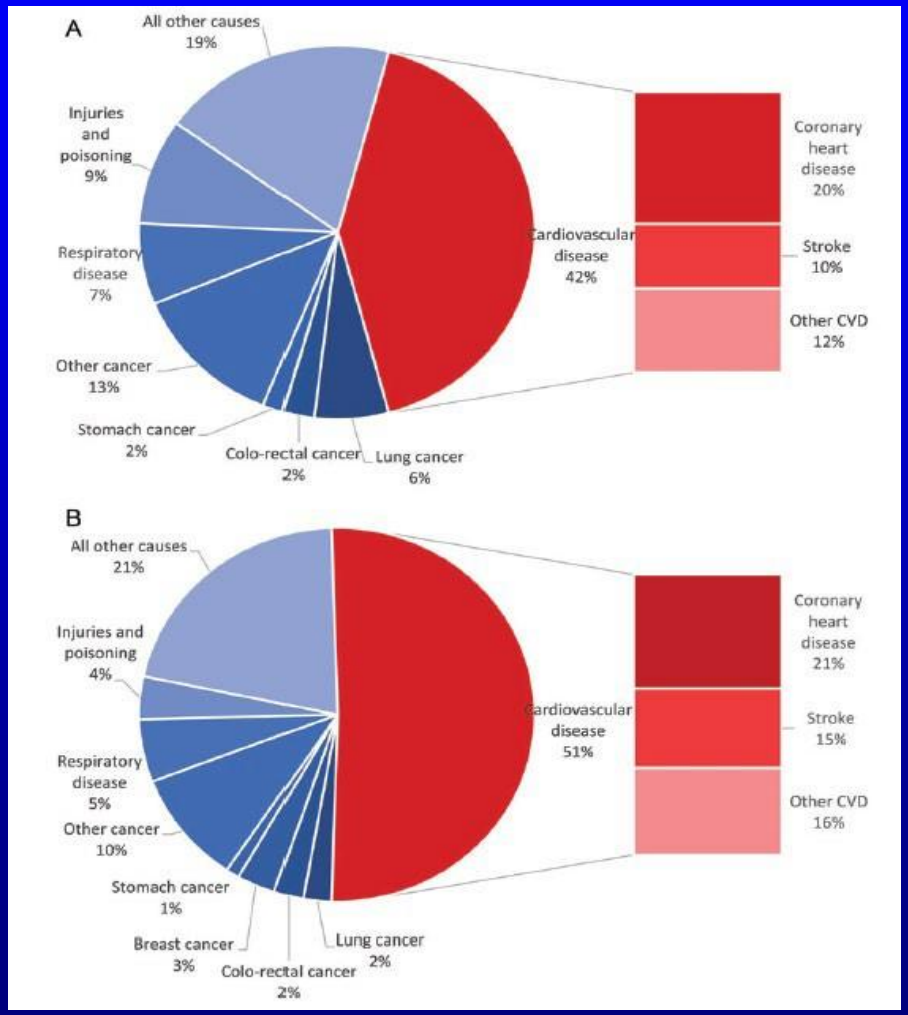
↓ ενεργοποίηση-
συσσώρευση
μακροφάγων

↓ μόρια προσκόλλησης
P-selectin
VLA4
ICAM-1

↑ ενεργοποίηση
αντιφλεγμονωδών
προστακυκλινών

Diamantis E et al. *Curr Cardiol Rev* 2017;13:209-216

# Cardiovascular disease in Europe 2014




**More than 4.000.000 deaths from cardiovascular disease**

Nichols M, et al. *Eur Heart J.* 2014;35:2950-9

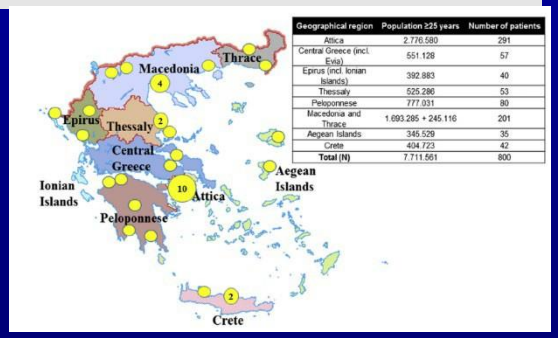
# Risk factors in patients with ACS: PHAETHON Study

Table 1 Baseline characteristics according to acute coronary syndrome type at hospital admission.

| Variable | STEMI (n=411) | Non-STEMI (n=303) | UA (n=86) | p-value |
|---|---|---|---|---|
| Age (years) | 61±12 | 65±13 | 63±11 | 0.001 |
| Gender, male (%) | 327(79.6%) | 231 (76.2%) | 68 (79.1%) | 0.557 |
| Hypertension | 218 (53.3%) | 195 (64.5%) | 57 (66.2%) | 0.003 |
| Hypercholesterolemia *52,5%* | 194 (47.3%) | 171 (56.8%) | 56 (66.6%) | 0.002 |
| Diabetes | 83 (20.3%) | 108 (36.3%) | 21 (24.7%) | <0.001 |
| Family history of CAD | 105 (25.7%) | 73 (24.4%) | 28 (32.5%) | 0.282 |
| History of CAD | 57 (13.9%) | 99 (33.0%) | 36 (41.8%) | <0.001 |
| Smokers (past or current) | 308 (74.9%) | 200 (66.0%) | 61 (70.9%) | 0.034 |
| Body mass index (kg/m$^2$) | 28.2±4.8 | 28.5±5.1 | 28.1±4.5 | 0.914 |
| Waist (cm)* | 101.4±13.8 | 102.4±13.8 | 99.5±12.8 | 0.257 |
| Metabolic syndrome* | 178 (53%) | 184 (68%) | 41 (53%) | <0.001 |
| Probability of in-hospital mortality based on GRACE (%)¶ | 2.25 (1.25–4.18) | 2.36 (1.22–4.76) | 0.80 (0.49–1.37) | <0.001 |
| Probability of 6-month mortality based on GRACE (%)¶ | 3.17 (1.77–5.66) | 5.32 (2.55–9.70) | 2.37 (1.48–4.80) | <0.001 |

*n=684, ¶n=682.

STEMI=ST-elevation myocardial infarction, NSTEMI=Non-ST elevation myocardial infarction, UA=unstable angina, CAD=Coronary Artery Disease.

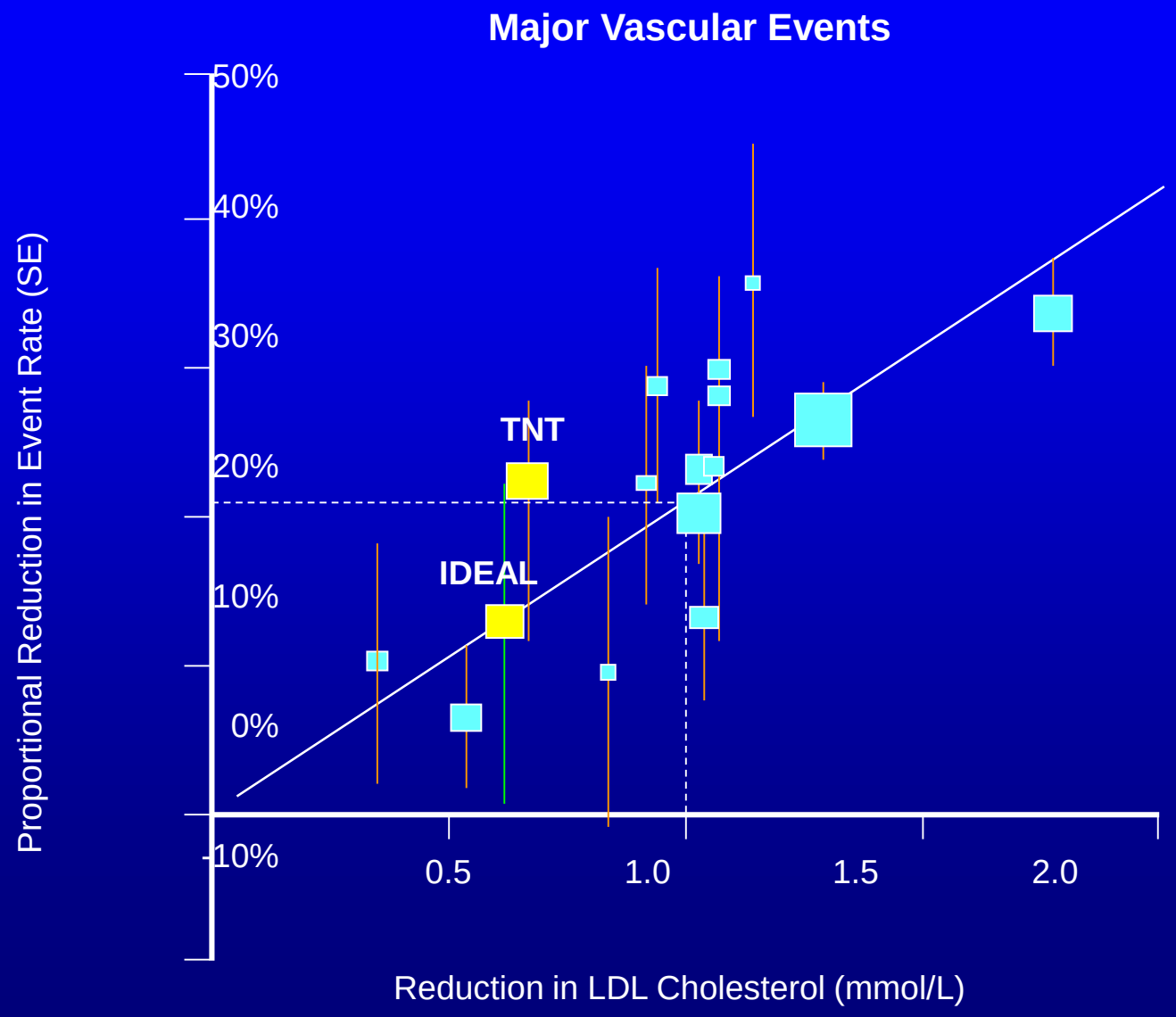



| Geographical region | Population ≥25 years | Number of patients |
|---|---|---|
| Attica | 2.776.580 | 291 |
| Central Greece (incl. Evia) | 551.128 | 57 |
| Epirus (incl. Ionian Islands) | 392.883 | 40 |
| Thessaly | 525.286 | 53 |
| Peloponnese | 777.031 | 80 |
| Macedonia and Thrace | 1.693.285 + 245.116 | 201 |
| Aegean Islands | 345.529 | 35 |
| Crete | 404.723 | 42 |
| **Total (N)** | 7.711.561 | 800 |

Andrikopoulos G. et al, Hellenic J Cardiol. 2016 May - Jun;57(3):157-166

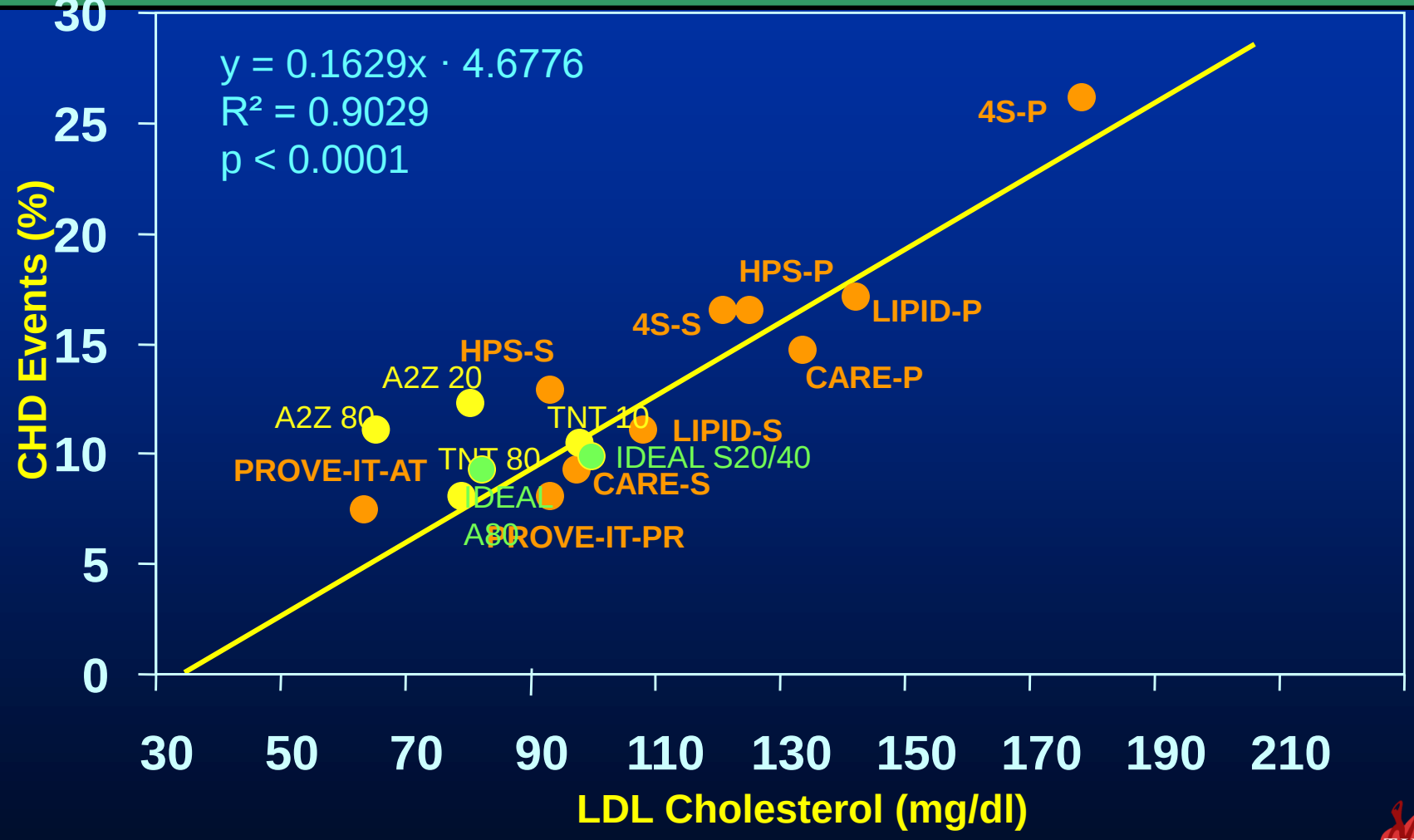
# Cholesterol Trialist Collaboration

## Meta-Analysis of Dyslipidemia Trials




Adapted from CTT Collaborators. *Lancet.* 2005; 366:1267-78

# CHD Event Rates in Secondary Prevention and ACS Trials




Updated from - O'Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

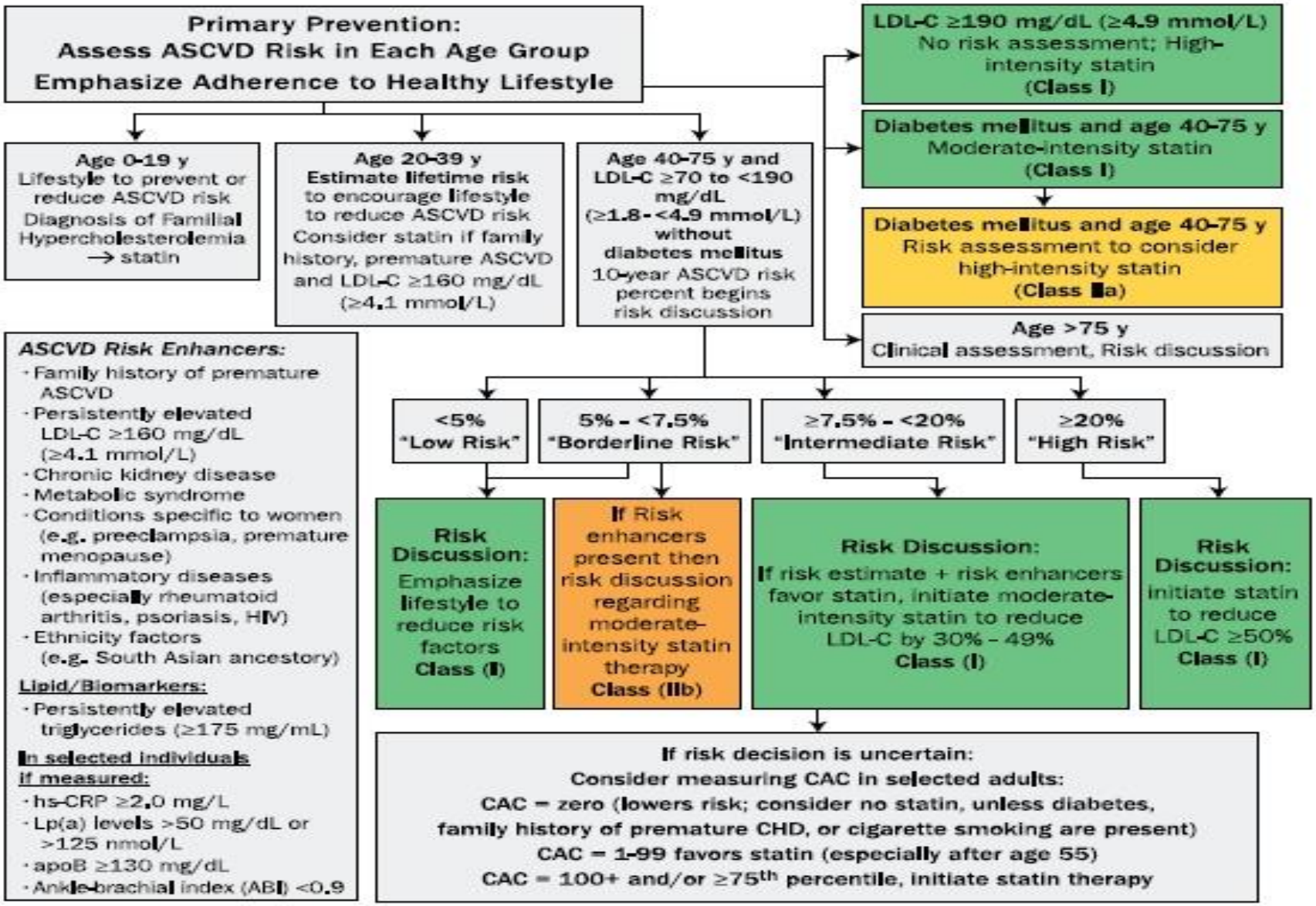
# 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

*GUIDELINES MADE SIMPLE*

*A Selection of Tables and Figure*

**ACC 2019**

## Primary Prevention

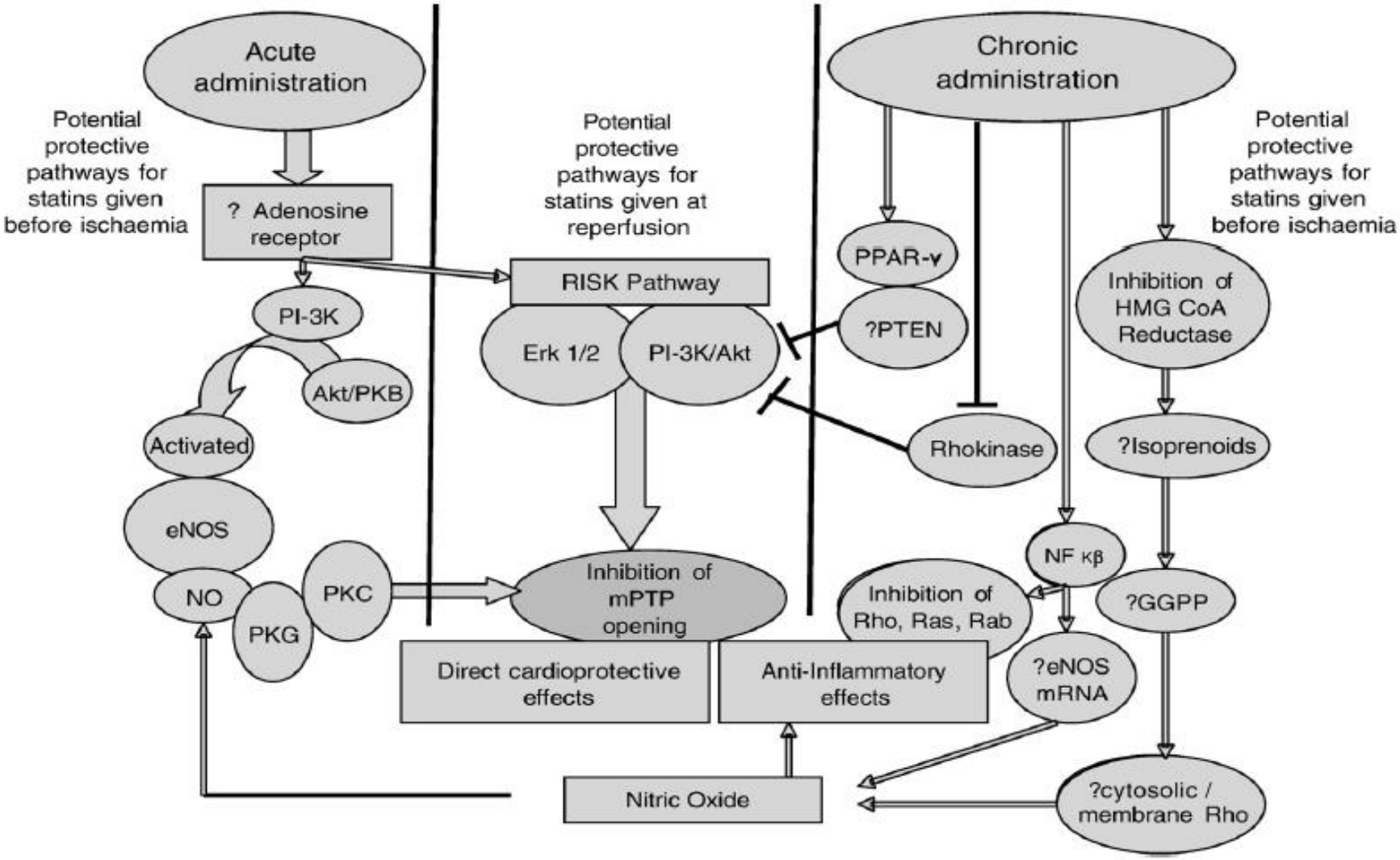


# Experimental studies for cardioprotection with statins

**Table 1**
Experimental cardioprotection with statin therapy given prior to myocardial ischaemia.

| Study | Experimental model | Treatment regime | Key results | Novel mechanistic insight |
|---|---|---|---|---|
| Pre-ischaemic cardioprotection elicited by statin therapy | | | | |
| Ueda et al., (1999) | Hypercholesterolaemic perfused rabbit hearts | Pre-treatment for 8 weeks with Pravastatin 5 mg/kg/day (orally). | Restoration of IPC protection in hypercholesterolaemic hearts but not in normal ones, associated with ecto-5′-nucleotidase activity. | Synergistic cardioprotective effect with IPC. |
| Lefer et al., (1999) | Perfused rat hearts. | Pre-treatment with 25 μg Simvastatin or Pravastatin 18 h prior IRI. Hearts perfused with PMNs. | ↑LV developed pressure ↓PMN infiltration ↓CD18 upregulation in PMN ↓PMN adherence to rat vascular endothelium ↓P-selectin expression. | Anti-inflammatory effect dependent on NO. |
| Scalia et al., (2001) | APO E−/− mice fed a high cholesterol diet subjected to in situ IRI. | Pre-treatment with a subcutaneous injection of 1 mg/kg Simvastatin 18 h prior to IRI. | Reduced myocardial infarct size. No effect on cholesterol. | Simvastatin able to cardioprotect an atherosclerotic animal heart model. Anti-inflammatory effect dependent on NO |
| Lefer et al., (2001) | In situ Db/Db murine heart | Pre-treatment for 5 days with intraperitoneal simvastatin (0.5 mg/kg daily). | Reduced myocardial infarct size. ↓PMN infiltration ↓PMN adherence to rat vascular endothelium | Simvastatin able to cardioprotect a type II diabetic animal heart model. Anti-inflammatory effect dependent on NO. |
| Kawabata et al., (2001) | Isolated rabbit hearts. | Pre-treatment with intravenous Pravastatin (0.025 mg/kg) 60 min prior to IRI. | Preserved ATP levels and maintained pH (MRI spectroscopy). These effects abolished by glibenclamide and L-NAME. | Pravastatin-induced cardioprotection of rabbit heart via $K_{ATP}$ channel and NO. |
| Di Napoli et al., (2001) | Perfused rat hearts | Simvastatin acutely before and during IRI at 10, 25, 50 and 100 μM. 15min I, 22–180min R. | Optimal results seen with 25 μM simvastatin. ↓CK in effluent. ↓vascular permeability. ↑eNOS mRNA and protein. ↓iNOS mRNA and protein. | Simvastatin provides cardioprotection via an eNOS dependent pathway. |
| Ikeda et al., (2003) | Perfused rat hearts | Pre-treatment Rosuvastatin (0.25 or 1.25 mg/kg) given 18 h prior to IRI. | ↑LV developed pressure ↓PMN infiltration ↓PMN adherence to rat vascular endothelium | Rosuvastatin able to cardioprotect rat hearts. Anti-inflammatory effect dependent on NO. |
| Lazar et al., (2003) | In situ pig heart | Pre-treatment with atorvastatin 40 mg daily given orally for 21 days | Less arrhythmias. Improved wall-motion scores Smaller infarct size No effect on cholesterol | Atorvastatin able to cardioprotect the pig heart when administered for 3 weeks. |
| Wolfrum et al., (2003) | In situ rat heart | Pre-treatment with Cerivastatin (0.3 mg/kg/d) for one week. | Smaller infarct. Increased eNOS and cardioprotection blocked by L-NAME. | Cerivastatin able to cardioprotect the rat heart. Protection dependent on eNOS. |
| Tiefenbacher et al. (2003) | In situ rat heart | Pre-treatment of Fluvastatin IV bolus (2 mg/kg) given 20 min prior to IRI. followed by IV infusion of 1 mg/kg/h. | ↑Regional wall thickening ↑myocardial blood flow and ↓Infarct size Protection abolished by L-NAME ↓myocardial MPO. | Fluvastatin able to acutely cardioprotect the rat heart. Anti-inflammatory effect dependent on NO. |
| Tavackoli et al., (2004) | In situ rat heart | Pre-treatment Simvastatin (20 mg/kg per day) for 3 days. | Smaller infarct size, protection blocked by glyburide. | Simvastatin-induced cardioprotection of rat heart via $K_{ATP}$ channel |
| Sanada et al., (2004) | In situ dog heart | Pre-treatment of IV bolus of Pravastatin (0.2, 2, or 10 mg/kg), Pitavastatin (0.01, 0.1, or 0.5 mg/kg), or Cerivastatin (0.5, 5, or 50 μg/kg) given immediately prior to IRI. | Smaller infarct size with protection blocked by wortmannin or 8-SPT given at reperfusion. | Cardioprotection of the canine heart requires activation of PI3 K-Akt and ecto-5′-nucleotidase activity at reperfusion. |
| Verma et al., (2004) | Cultured human ventricular cardiomyocytes subjected to simulated IRI. | Pravastatin (1, 10, and 100 μM) added to the hypoxic/reoxygenation buffers. | Reduced cardiomyocyte death. Protection blocked by bosentan, L-NAME and was associated with production of NO and Akt phosphorylation. | Pravastatin able to cardioprotect isolated human ventricular cardiomyocytes through ET-1, Akt and NO. |
| Birnbaum et al., (2005) | In situ rat heart | Pre-treatment with atorvastatin 10 mg/kg/day (oral gavage) prior to IRI. | Smaller infarct size with protection blocked by COX-2 inhibitor. Protection associated eNOS and iNOS phosphorylation as well as prostaglandin production. | Cardioprotection of the rat heart requires COX-2 activation and prostaglandin release. |
| Di Napoli et al., (2005) | Isolated rat hearts | Oral treatment with Rosuvastatin (0.2–20 mg/kg) for 3 weeks. | Less myocardial dysfunction, endothelial dysfunction and mitochondrial damage. | NO dependent effects on vascular endothelium and myocardium. |
| Mensah et al., (2005) | Isolated rat heart | Oral gavage for 1, 3 days and 1 or 2 weeks with oral 20 mg/kg atorvastatin. Supplemental dose of 40 mg/kg given prior to IRI. | Reduced infarct size with 1 or 3 days treatment but not 1 or 2 weeks treatment. Protection recaptured if acute atorvastatin 40 mg given prior to IRI | Cardioprotective effect of atorvastatin wanes with chronic dosing possibly due to down-regulation of PI3 K-Akt pathway by PTEN. Possible to recapture protection with acute high dose of atorvastatin. |

# Pleiotropic effects of statins



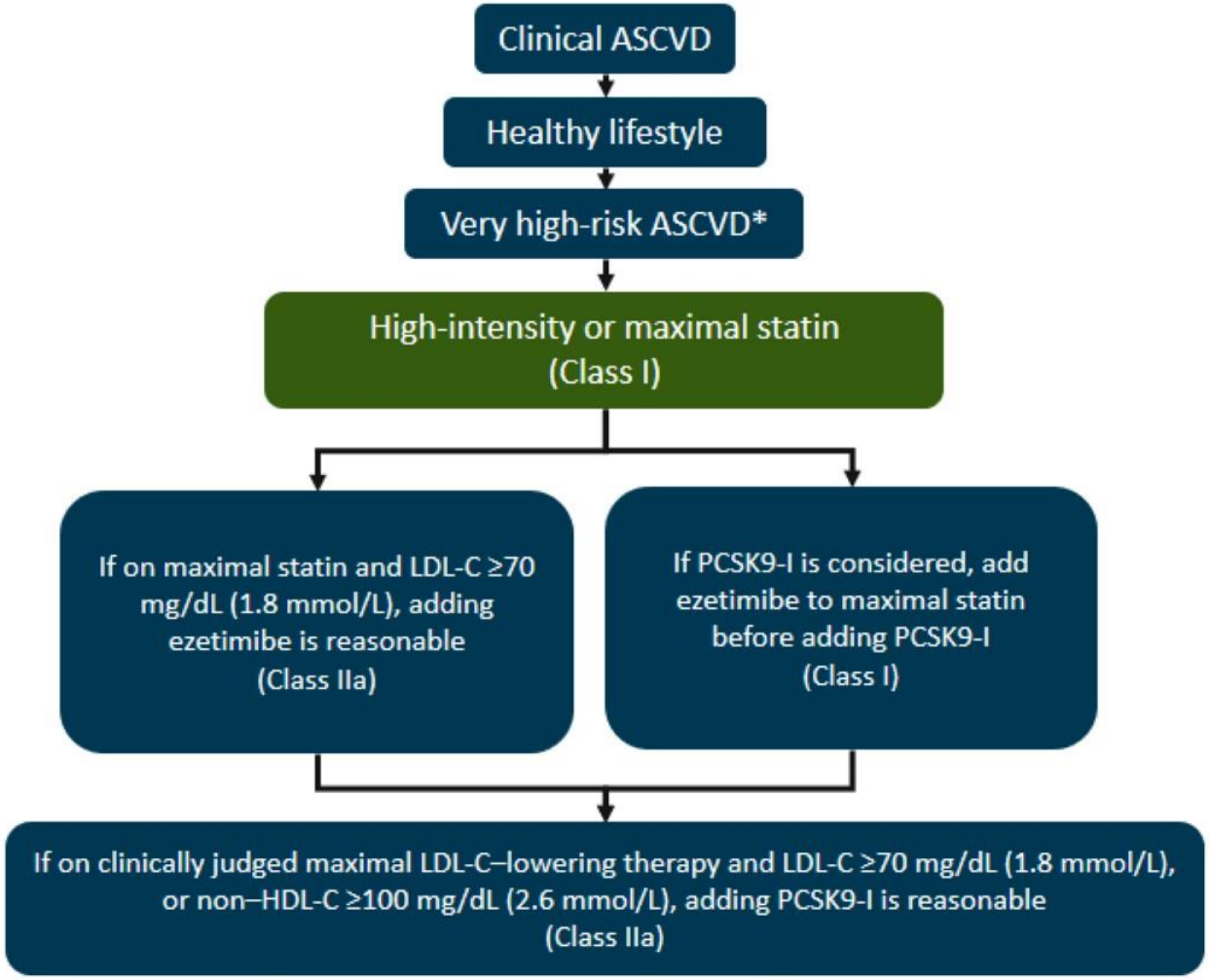
# Statins and PCI

**Table 3**
Statin therapy and percutaneous coronary intervention.

| Study | Study design | Number and type of patients | Intervention | Follow up | Outcomes |
|---|---|---|---|---|---|
| *Elective PCI* | | | | | |
| Bertrand et al. (1997) | Multi centre, randomised, placebo controlled | 695 patients having undergone successful balloon angioplasty (no stent) | Pravastatin 40 mg/d or placebo started after coronary intervention | 6 months | No difference in luminal diameter or rate of restenosis. No difference in clinical outcomes. |
| Serruys et al. (1999) | Randomised, placebo controlled, double blind | 1054 patients undergoing elective coronary artery balloon angioplasty (no stent) | 40 mg twice/d fluvastatin or placebo started 2–3 weeks pre-PTCA | Angiographic restenosis at 26 weeks and MACE outcomes at 4.0 weeks. | No effect on restenosis. Death and MI reduced from 4 to 1.4% (log rank $p = 0.025$) |
| Schartl et al. (2001) | Open label, randomised, multi centre | 131 patients following PCI | Atorvastatin or usual care. Atorvastatin titrated to achieve LDL-C< 100 mg/dL | Plaque volume at 12 months | A non-significant reduction in plaque volume. No difference in MACE rates. |
| Serruys et al. (2002) | Randomised, placebo controlled, double blind | 1677 patients who had undergone first successful PCI | 80 mg/d fluvastatin or placebo started at hospital discharge | Survival time free from MACE at a median follow up of 3.9 years. | Significant reduction in MACE rates in fluvastatin group. RR 0.78 (95% CI 0.64 to 0.95, $p = 0.01$) |
| Pasceri et al. (2004) | Randomised, placebo controlled, double blind | 153 statin naive patients undergoing elective PCI | 40 mg/d atorvastatin or placebo started 7 days prior to procedure. | Post procedural peak levels of CK-MB, Trop-I and Myoglobin. | Atorvastatin significantly ↓ myocardial enzyme release post elective PCI. |
| Brigouri et al. (2004) | Randomised | 451 patients due to undergo elective PCI | Randomised to statin (variable type) or no statin | Incidence of large peri-procedural myocardial injury (CK-MB and Trop-I ↑ ≥5 times ULN) at 6 and 12 h post PCI | ↓ incidence of CK-MB release 5× ULN, and ↓ incidence of Trop I 5× ULN (32 to 23.5%, $p = 0.043$). |
| Mood et al. (2007) | Meta-analysis | 3941 patients undergoing elective PCI | Randomised to statin (variable type) started periprocedure | Clinical outcomes from 1 day to 45 months | ↓ incidence of myocardial infarction post PCI (0.57, 95%CI 0.42 to 0.78, $p = 0.0001$) |
| *Urgent PCI* | | | | | |
| Chang et al. (2004) | Observational | 119 patients undergoing urgent PCI following ACS | statins or no statin therapy | Myocardial injury measured by CK-MB or CK ≥ 3 times ULN. MACE over 6 months | ↓ Myocardial injury 10 to 2% ($p = 0.04$). ↓ MACE 21 to 17% ($p = 0.015$) |
| Chyrchel et al. (2006) | Randomised, open label | 140 patients undergoing urgent PCI following ACS | 80 mg atorvastatin daily started 3 days prior to PCI and then 40 mg daily or just 40 mg daily started after PCI | MACE rates over approx. 600 days | ↓ composite endpoint of death, MI & re-PCI rates from 25.9 to 8.1% ($p = 0.006$) |
| Patti et al. (2007) | Multi centre, randomised, placebo controlled, double blind | 171 patients undergoing urgent PCI following ACS | 80 mg atorvastatin 12 h prior to PCI with 40 mg just prior and continuing or placebo until after PCI and then atorvastatin 40 mg started | 30 day MACE rates. Peri-procedural myocardial injury defined by twice the ULN of CK-MB, Trop I or a 2 fold increase. | ↓ MACE (OR 0.12, 95%CI 0.05 to 0.5, $p = 0.004$). ↓ incidence of CK-MB release 7% v 27% ($p = 0.001$). ↓ incidence of Trop I release 41% v 58% ($p = 0.039$). |
| *Elective and urgent PCI* | | | | | |
| Chan et al. (2002) | Observational | 5052 patients undergoing elective and urgent PCI (recent MI excluded) | 26.5% of patients taking variable statins pre-procedure. | Mortality at 30 days and 6 months. | ↓ unadjusted 30 mortality from 1.5 to 0.8% (HR 0.53, log rank $p = 0.048$). ↓ unadjusted 6 months mortality from 3.6 to 2.4% (HR 0.67, log rank $p = 0.046$) |
| Chan et al. (2003) | Observational | 1552 patients undergoing elective or urgent PCI | 39.6% of patients taking variable statins pre-procedure. | Level of hsCRP and peri-procedural MI (defined as CKMB >3 times ULN) | statin use associated with ↓ hsCRP (0.4 v 0.5, $p = 0.012$). statins ↓ peri-procedural MI (5.7 v 8.1% $p = 0.038$) |
| Merla et al. (2007a) | Meta-analysis | 4751 patients undergoing all types of PCI | Observational and randomised studies | Incidence of peri-procedural myonecrosis | Incidence of myonecrosis reduced from 17.5% to 9% |

# 2018 ACC/AHA Guidelines on the Management of Blood Cholesterol

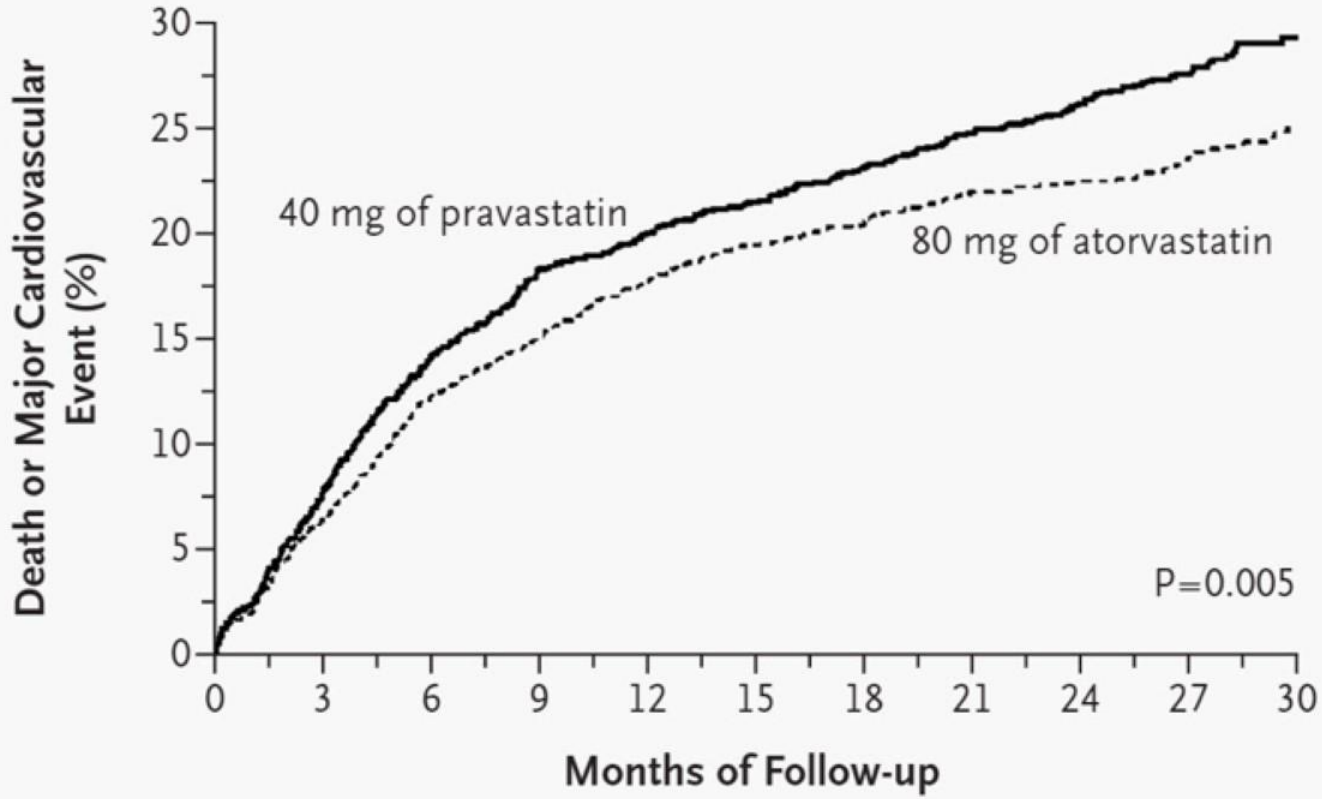
*Secondary Prevention – Statins*




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

Grundy SM, et al. *Circulation*. 2018. [Epub ahead of print].

# Impact of Statin Intensity on CV Outcomes Post-ACS




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Pravastatin | 2063 | 1688 | 1536 | 1423 | 810 | 138 |
| Atorvastatin | 2099 | 1736 | 1591 | 1485 | 842 | 133 |

Cannon CP, et al. *N Engl J Med*. 2004;350:1495-1504.

# ARMYDA-ACS (Atorvastatin for Reduction of MYocardial Damage during Angioplasty- Acute Coronary Syndromes ) trial

## Multicenter, randomized, double blind, prospective study evaluating effects on outcome of atorvastatin pre-treatment in patients with Acute Coronary Syndromes undergoing early PCI


*Chairman of the Study:* **Germano Di Sciascio**

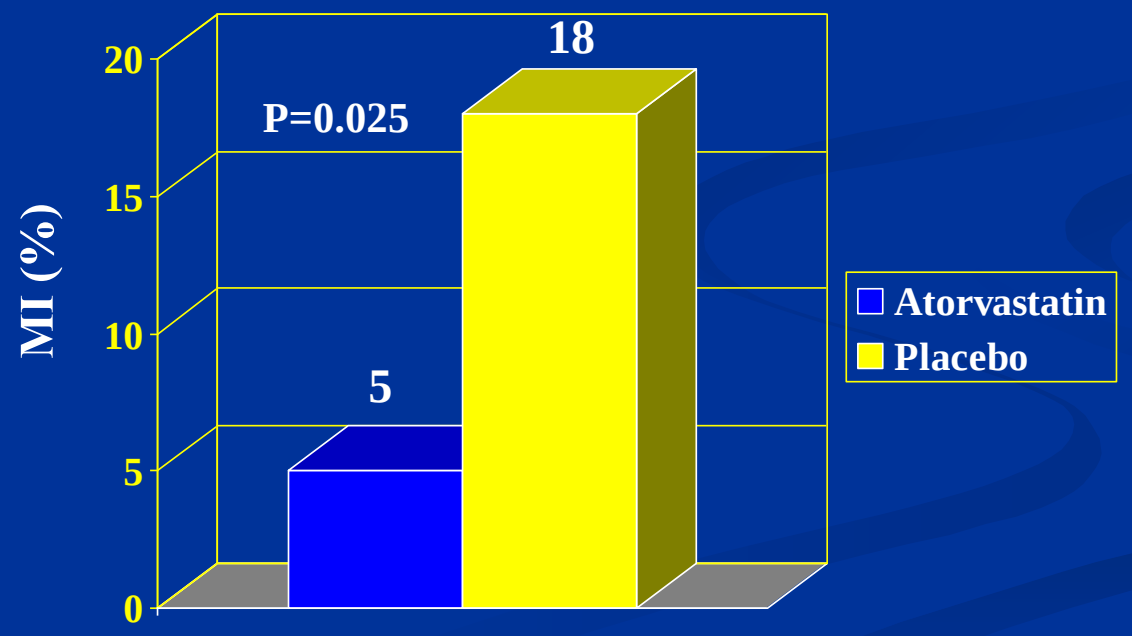
*Principal Investigators:* **Giuseppe Patti, Vincenzo Pasceri, Rino Sardella, Giuseppe Colonna**

*Investigators:* **Antonio Montinaro, Marco Miglionico, Luigi Fischetti, Andrea D'Ambrosio, Annunziata Nusca, Giordano Dicuonzo, Bibi NGuyen, Laura Gatto, Fabio Mangiacapra**

# BACKGROUND

❖ The original ARMYDA trial demostrated that 7-day pretreatment with atorvastatin (40 mg/day) confers 81% risk reduction of peri-procedural MI in patients with Stable Angina undergoing elective PCI

*Primary end point: Incidence of MI*




Pasceri V, Patti G, Di Sciascio G, et al. Circulation 2004;110:674-678

# BACKGROUND

❖ Efficacy of statin pretreatment in patients with ACS undergoing early PCI has not characterized

❖ An observational study on 119 pts has suggested that patients with ACS who were already receiving statins at the time of intervention have a lower incidence of peri-procedural myonecrosis; however, patients were treated with different types of statins, variable doses and unknown duration of previous treatment, and those findings have not been validated in a randomized trial.

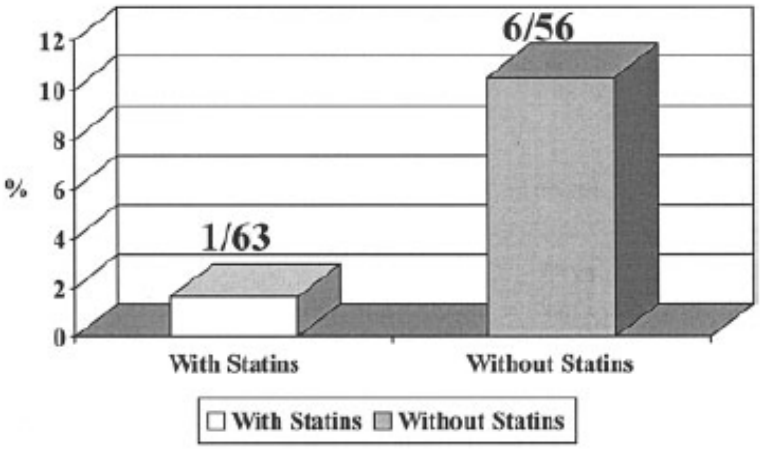



Fig 1. Incidence of periprocedural myonecrosis.

Chang SM, et al. Cathet Cardiovasc Interv 2004

# ARMYDA-ACS: CONCLUSIONS

- The ARMYDA-ACS trial indicates that even a short-term atorvastatin pretreatment prior to PCI may improve outcome in patients with Unstable Angina and NSTEMI.

- This benefit is mostly driven by a reduction of peri-procedural MI (70% risk reduction)

- Lipid-independent pleiotropic actions of atorvastatin may explain such effect

- These findings may support the indication of "upstream" administration of high dose statins in patients with Acute Coronary Syndromes treated with early invasive strategy

# ARMYDA-ACS trial

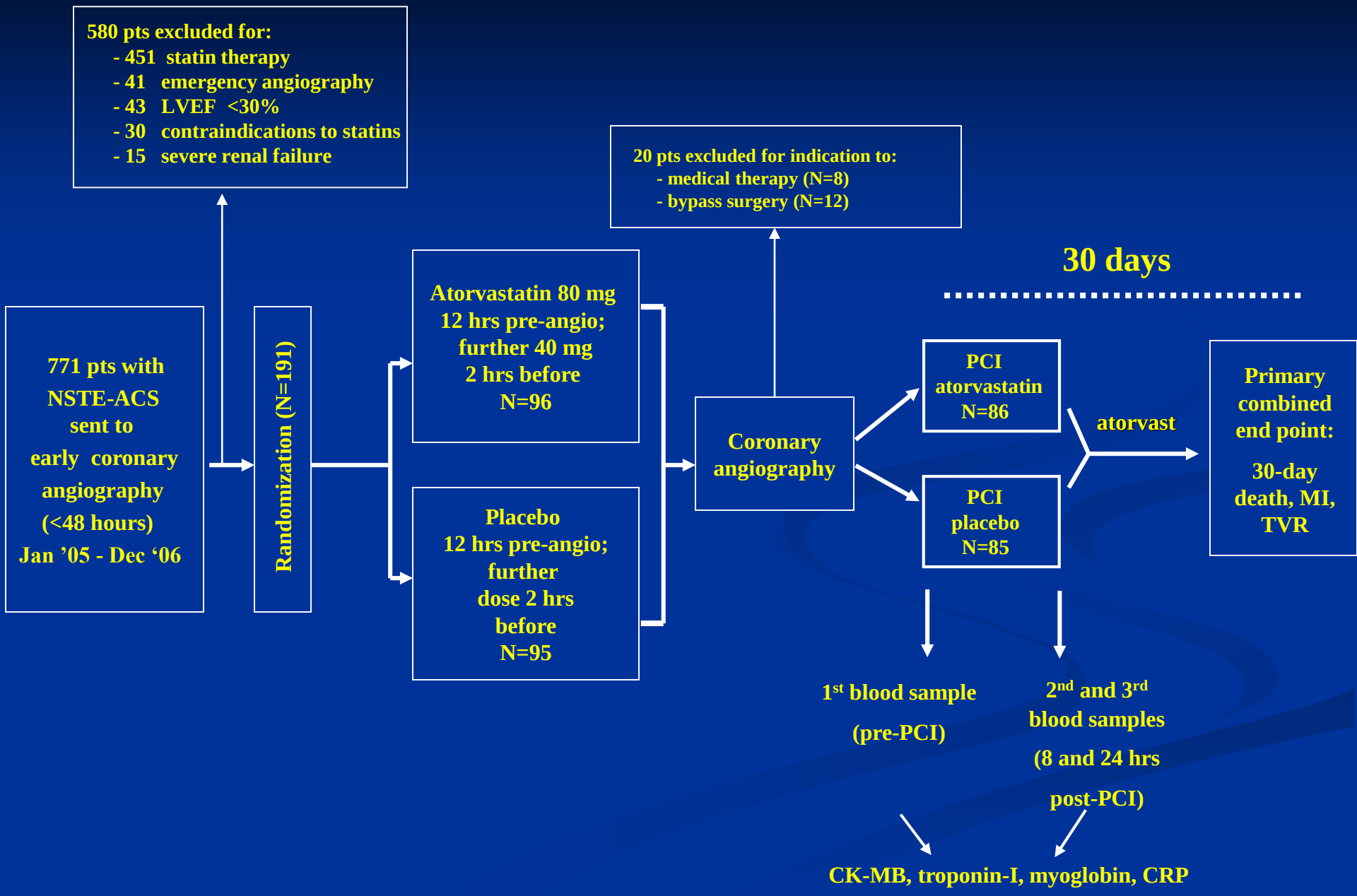
## Inclusion criteria:

- ✓ NSTE-ACS undergoing early angiography (<48 hrs)

## Exclusion criteria:

- ✓ STEMI
- ✓ ACS with high risk features warranting emergency angiography
- ✓ Previous or current statin therapy
- ✓ LVEF <30%
- ✓ Contraindications to statins (liver or muscle disease)
- ✓ Severe renal failure (creatininine >3 mg/dl)

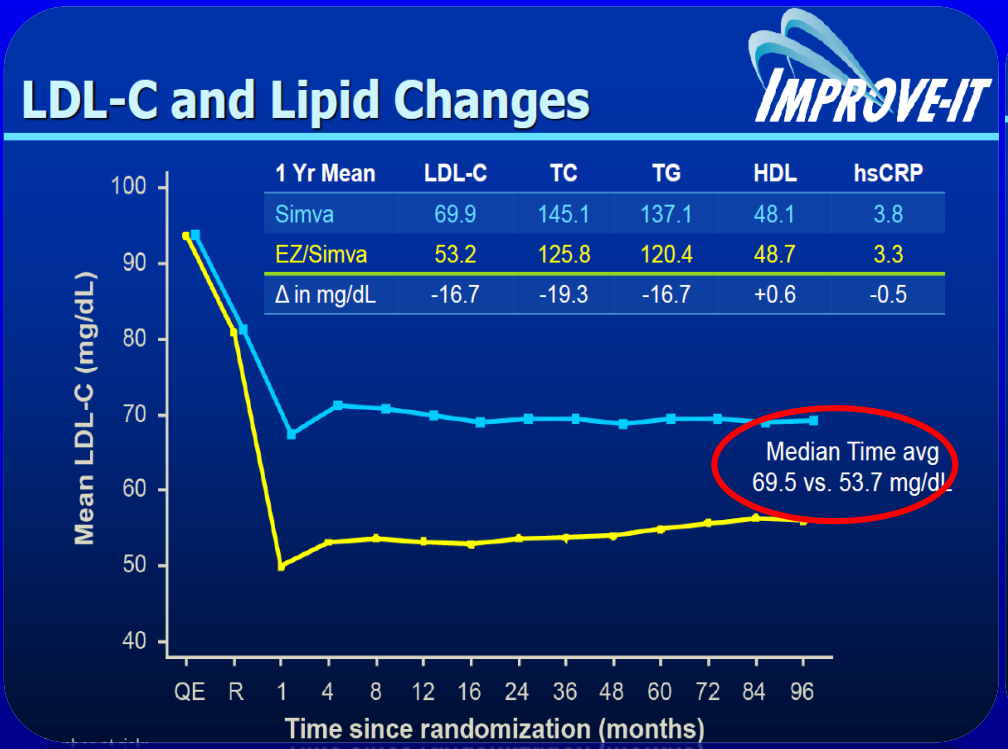
# ARMYDA-ACS trial: Study design

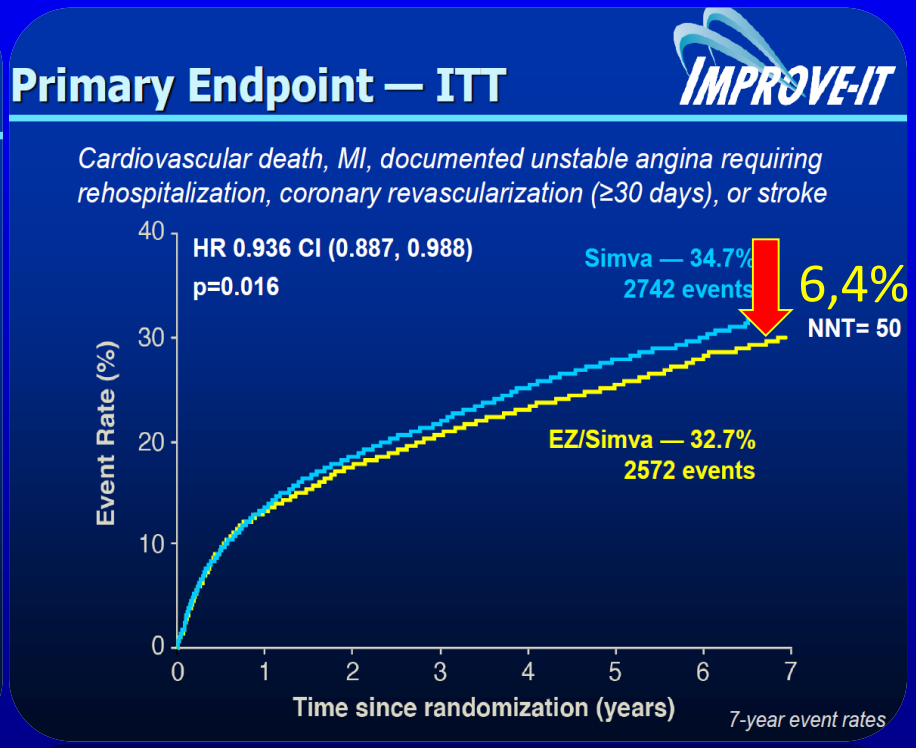


# Statins in acute Coronary syndromes

| Study | Study design | Number and type of patients | Intervention | Follow up | Outcomes |
|---|---|---|---|---|---|
| Arntz et al., (2000) | Prospective, open label, randomised | 135 patients undergoing PCI following new Q wave infarction or ACS | Pravastatin started at 20 mg/d and titrated for LDL-C < 130 mg/dl or standard care by family physician | Angiographic minimal luminal diameter and MACE rates at 6 and 24 months | ↓rate of progression of coronary atherosclerosis. ↓MACE rates, OR 3.6, 95%CI 1.6 to 7.8, $p = 0.005$) |
| Kayikcioglu et al., (2002) | Randomised, placebo controlled | 164 patients having been thrombolysed for acute MI | Pravastatin 40 mg or placebo | Clinical outcomes at 6 months | ↓rate of subsequent angina, 59.5% to 30% ($p = 0.018$), ↓composite MACE, 75.6% to 32.5% ($p = 0.0001$). |
| Okazaki et al., (2004) | Randomised, open label | 70 patients following an ACS and PCI | 20 mg atorvastatin or control (lipid lowering diet and cholesterol absorption inhibitor) | Atherosclerotic plaque volume at 6 months, MACE rates. | Significant reduction in plaque volume. No difference in MACE rates. |
| Cannon et al., (2004) | Multi-centre, randomised, double blind, placebo controlled | 4162 patients following ACS | Atorvastatin 80 mg aiming LDL-C < 70 mg/dl or pravastatin 40 mg aiming LDL-C < 100 mg/dl | MACE rates over average 2 year follow up. | Relative risk reduction in composite MACE of 16% (95% CI 5 to 26%, $p = 0.005$) in atorvastatin group |
| de lemos et al., (2004) | Multi-centre, randomised, double blind, placebo controlled | 4497 patients | Simvastatin 40 mg and then 80 mg or placebo for one month and then simvastatin 40 mg | MACE rates over 4 months and 2 years. | No reduction in MACE at 4 months. At 2 years rate of cardiovascular death ↓from 5.4 to 4.1% ($p = 0.05$). |
| Colivicchi et al., (2002) | Prospective, randomised | 81 patients following ACS not amenable to revascularisation | Atorvastatin 80 mg or conventional treatment | 12 month MACE rates | ↓MACE from 46 to 22% (OR 0.33, 95%CI 0.12 to 0.88, $p = 0.0025$) |
| Schwartz et al., (2001) | Multi-centre, randomised, double blind, placebo controlled | 3086 patients following an ACS | Atorvastatin 80 mg or placebo to start 24 to 96 h after admission | MACE rates over 16 weeks | ↓recurrent ischaemia requiring hospitalisation from 8.4 to 6.2% ($p = 0.02$). No difference in other MACE outcomes. |
| Liem et al., (2002) | Randomised, placebo controlled, double blind | 540 patients following an ACS | Fluvastatin 80 mg daily started within 2 weeks of event | Observed ischaemia and MACE rates over 12 months | No difference in observed ischaemia, no difference in MACE |
| Thompson et al., (2004) | Randomised, placebo controlled, double blind | 3408 patients following an ACS | Pravastatin 20 to 40 mg or placebo | MACE rates at 30 days | Non-significant trend to benefit of pravastatin. |
| Lenderink et al., (2006) | Retrospective cohort | 10,484 patients following an ACS | statin naive survivors at 24 h receiving statins versus those not. | All cause mortality at 7 and 30 days. | ↓7 day mortality (0.4%v2.6%, unadjusted HR 0.16, 95% CI 0.08 to 0.37). Non-significant ↓mortality at 30days. |
| Briel et al, (2006) | Meta-analysis of randomised controlled trials | 13,024 patients following an ACS | Variety of statins and doses started within 14 days | MACE outcomes at 1 and 4 months | No reduction in death, MI or CVA up to 4 months. |
| Aronson et al., (2008) | Prospective observational study | 1,563 patients following acute MI | statin started in-hospital pre-discharge (type and dose not recorded) or not | Admission with heart failure over median follow up of 17 months. | Pre-discharge statin therapy ↓ admission with heart failure from 14.8 to 6.5% ($p < 0.0001$). |

# IMPROVE-IT: the LDL-lowering strategy




Cannon CP. N Engl J Med 2015;372:2387-97

# REVERSAL Trial

502 symptomatic coronary artery disease patients with elevated LDL

Randomized, double-blind, multicenter

**Aggressive lipid lowering strategy**
- Atorvastatin (80 mg)
- n=253

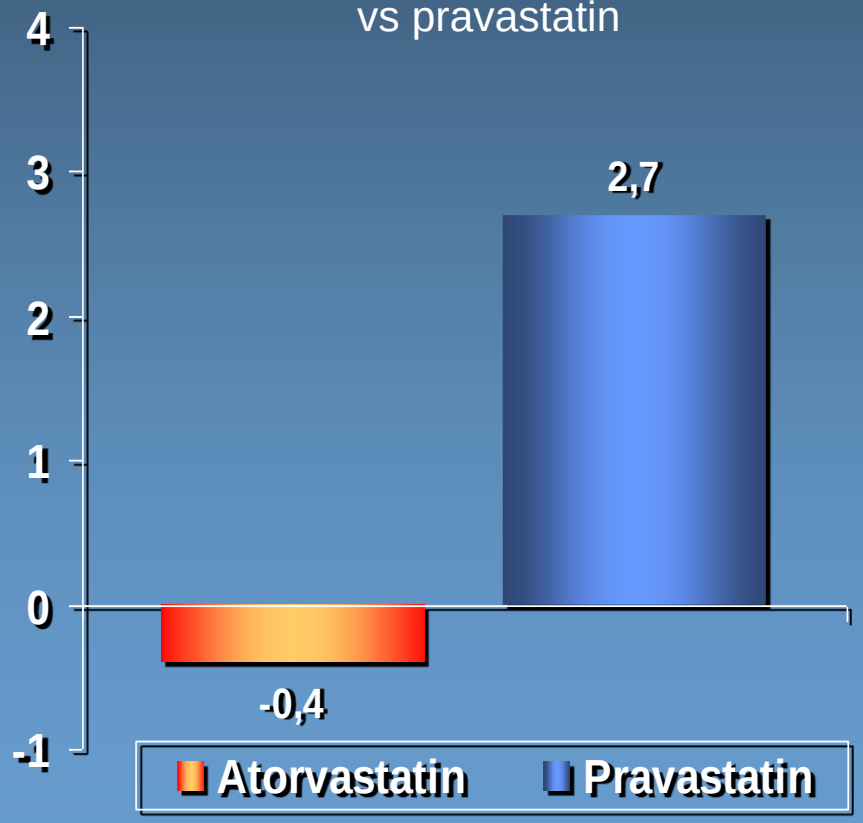
**Moderate lipid-lowering strategy**
- Pravastatin (40 mg)
- n=249

Endpoints (follow-up 18 months):
- Primary – Percent change in atheroma volume on IVUS between baseline and 18 month follow-up
- Secondary – Absolute change in atheroma volume; change in the percent obstructive volume

# REVERSAL Trial

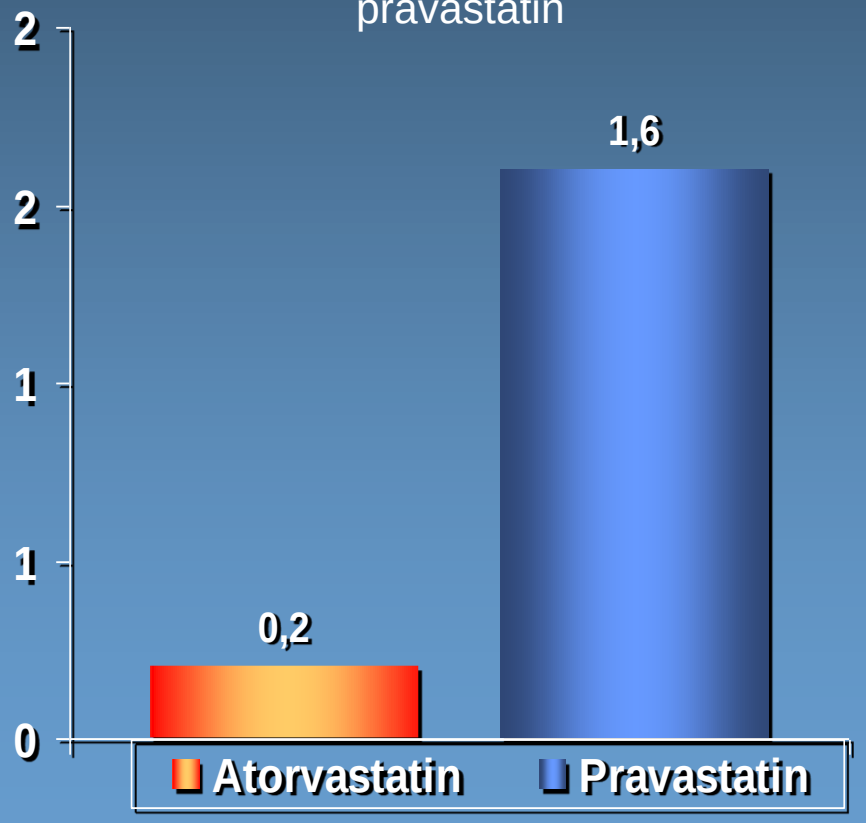
## Change in atheroma volume

p=0.02 for change between atorvastatin vs pravastatin




## Change in percent obstruction volume

p=0.0002 for change between atorvastatin vs pravastatin



# REVERSAL Trial

- Among patients with symptomatic CAD and elevated LDL, use of an aggressive lipid-lowering strategy through treatment with 80-mg atorvastatin was associated with a reduction in percent change in atheroma volume compared with a more moderate lipid-lowering strategy through treatment with 40-mg pravastatin
- Primary endpoint used an IVUS endpoint and the trial was not designed to assess mortality or clinical events, and a much larger trial would be needed to assess superiority of one statin over another for these endpoints
- AHA/ACC guidelines currently recommend statin therapy (as a class) for reduction of LDL levels to <100 mg/dL

# The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial: a new frontier for statins?

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Aggressive lowering of the LDL-C can was associated with a reduction in recurrent acute coronary ischemia at 16 weeks. This is consistent with improved endothelial function and possibly accelerated healing of ruptured plaque. Unfortunately the study only tested very high-dose atorvastatin and not the value of lower doses and the effect of other agents such as ACE inhibitors. The 16-week cost of treatment with atorvastatin is estimable at about $34,000 per event prevented. In an accompanying editorial, Frank Sacks observed: 1) since there was no association between outcome and baseline or on treatment LDL-C within the treatment arm, the standard 10 mg dose of atorvastatin may have been as effective; 2) the results were of borderline significance and the 11 patients lost to follow-up could have influenced the data. Nevertheless, the study lends support for statin therapy to be considered in all patients discharged from the hospital with an acute coronary syndrome including MI.

# PROVE-IT STUDY

## Methods

This study randomized 4,126 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days. The goal of the study was to establish the non-inferiority of pravastatin versus atorvastatin in terms of the time to an end-point event. Standard therapy of pravastatin, 40 mg/day, was compared with intensive therapy of atorvastatin, 80 mg/day.

The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization) and stroke. Followup lasted 18 to 36 months, with the mean being 24 months.

## Results

Patients receiving pravastatin achieved a median low-density lipoprotein cholesterol (LDL-C) of 2.46 mmol/L, compared to an LDL-C level of 1.60 mmol/L achieved in the high-dose atorvastatin group ($p < 0.001$).

Estimates of the rates of the primary end point at two years were 26.3% and 22.4% in the pravastatin and atorvastatin groups, respectively, reflecting a 16% reduction in the hazard ratio in favour of atorvastatin ($p = 0.005$).

The authors concluded that an intensive, lipid-lowering statin regimen is superior to a standard regimen in providing protection against death or major cardiovascular events among patients who have recently had an acute coronary syndrome. Furthermore, these findings indicate such patients benefit from early and continued lowering of LDL-C to levels substantially below current targets.

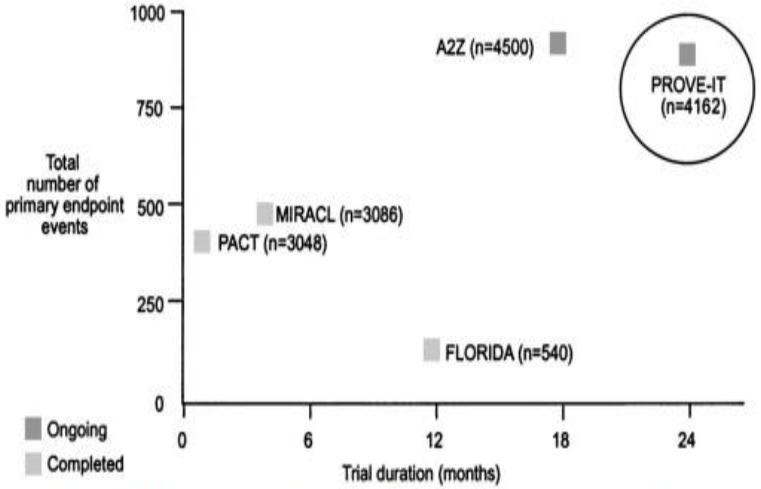


FIGURE 6. PROVE-IT TIMI 22 is superior to previous or ongoing statin trials in ACS, because it has the combination of the longest duration and the highest number of end points (http://www.timi.org, http://www.clinicaltrialresults.org).

# Statin therapy and cardiac surgery

Statin therapy and cardiac surgery.

| Study | Design | Type of patients (No) | Intervention | Follow up | Outcome |
|---|---|---|---|---|---|
| Pan et al., (2004) | Retrospective cohort | 1663 patients undergoing primary CABG | Pre-operative statin or not. | 30 days | ↓ all cause mortality from 3.75% to 1.8% ($p<0.05$). ↓ all cause mortality and stroke from 7.1% to 4.6% ($p<0.05$). |
| Ali et al., (2005) | Retrospective cohort (with matched propensity model analysis) | 5469 patients undergoing primary CABG | Pre-operative statin or not. | In-hospital outcome | No significant difference between matched groups in mortality or other measures. |
| Collard et al, (2006) | Pre-specified subset analysis of a prospective longitudinal study | 2666 patients undergoing primary elective CABG | Pre-operative statin or not. | Hospital stay | ↓cardiac mortality in first 3 post-operative days (0.3% v 1.4%, $p=0.03$). No reduction of in-hospital MI. |
| Chello et al., (2007) | Randomised, placebo controlled | 30 patients undergoing on-pump CABG | Simvastatin 40 mg or placebo started 3 weeks pre-op | N/A | ↓ IL-6 and IL-8. ↑ neutrophil apoptosis |
| Fedoruk et al., (2008) | Retrospective cohort | 447 patients undergoing isolated cardiac valve surgery | Pre-operative statin or not | 30 days | Adjusting for risk factors- composite outcome of 30 day mortality/stroke/renal failure ↓with OR 2.7 (95% CI 1.24-5.66, $p=0.012$) |
| Liakopoulos et al., (2008) | Meta-analysis | 30,000+ patients undergoing cardiac surgery. | Variable types of preoperative statin or not. | Variable | A 1.5% absolute reduction in early all cause mortality. Reduced peri-operative stroke and AF. No reduction in peri-operative MI or renal failure. |

# Statin therapy a non –cardiac surgery

**Table 6**
Statin therapy and non-cardiac surgery.

| Study | Study design | Number and type of patients | Intervention | Follow up | Outcomes |
|---|---|---|---|---|---|
| Poldermans et al., (2003) | Retrospective case controlled | 2816 patients undergoing major vascular surgery. | 160 cases matched with 320 controls Analysis of statin use. | 30 day mortality | Significantly ↓mortality rate in statin uses against controls (OR 0.22, 95 CI 0.1 to 0.47) |
| Kertai et al., (2004) | Retrospective cohort | 570 patients undergoing elective AAA repair | Analysis of pre-op statin and β-blocker use or not. | In hospital and 30 day mortality and MI | statin use independently associated with ↓mortality or post-op MI (OR 0.24, 95% CI 0.1 to 0.7, $p=0.01$) |
| Lindenauer et al., (2004) | Retrospective cohort | 780,591 patients undergoing major non-cardiac surgery. | 70,159 statin users with matched propensity analysis | In hospital mortality | statin use assoc. with ↓crude mortality from 3.05 to 2.13% ($p=0.001$). |
| Durazzo et al. (2004) | Prospective, randomised, placebo controlled, double blind | 100 patients undergoing major vascular surgery. | 20 mg atorvastatin for a mean of 30 days pre-op or placebo. | 6 months | ↓ adverse cardiac events from 26 to 8% ($p=0.031$). |
| O'Neil-Callahan et al., (2005) | Retrospective cohort | 1163 patients who had undergone major vascular surgery | Pre-operative statin or not | In hospital | ↓peri-op cardiac events from 16.5 to 9.9% ($p=0.001$). Mainly ↓myocardial ischaemia. |
| Feringa et al., (2007) | Prospective non-randomised. | 359 patients undergoing elective major vascular surgery. | Pre-operative statin therapy or not. Variety of types and doses | 30 days and longer (mean 2.3 years) | Higher statin doses significantly ↓post-op Troponin T release. statins significantly ↓ 30 day and late post-operative cardiac events. |
| Poldermans, 2008 (Unpublished) | Prospective, randomised, placebo controlled, double blind | 497 patients scheduled to undergo vascular surgery | 80 mg fluvastatin extended release or placebo started pre-operatively | 30 days | ↓ myocardial ischaemia from 18.9% to 10.9% (OR 0.53; 95%CI 0.32-0.88). ↓ cardiovascular death or non-fatal MI from 10.1% to 4.8% (OR 0.48; 95% CI 0.24-0.95) |

# Xanthelasma

# In conclusion

- **Statins** are established as playing a major role in cardiovascular disease in almost all categories of patient risk.

- The **'pleiotropic' effects** of statins continue to reveal further potential benefits in a diverse range of interventional settings. The benefit of using statins acutely prior to scenarios where myocardial injury may be expected and in emergent situations is slowly being realised.

The **potential benefits** of limiting myocardial injury in these settings are evident and further work is needed to clarify the optimum statin regimen in different settings and the mechanisms behind the cardioprotective actions. Whether or not further cardioprotective effects can be gained by additional acute doses of statins has exciting potential and merits