# The Role and Clinical Benefit of Add-on Ezetimibe Treatment

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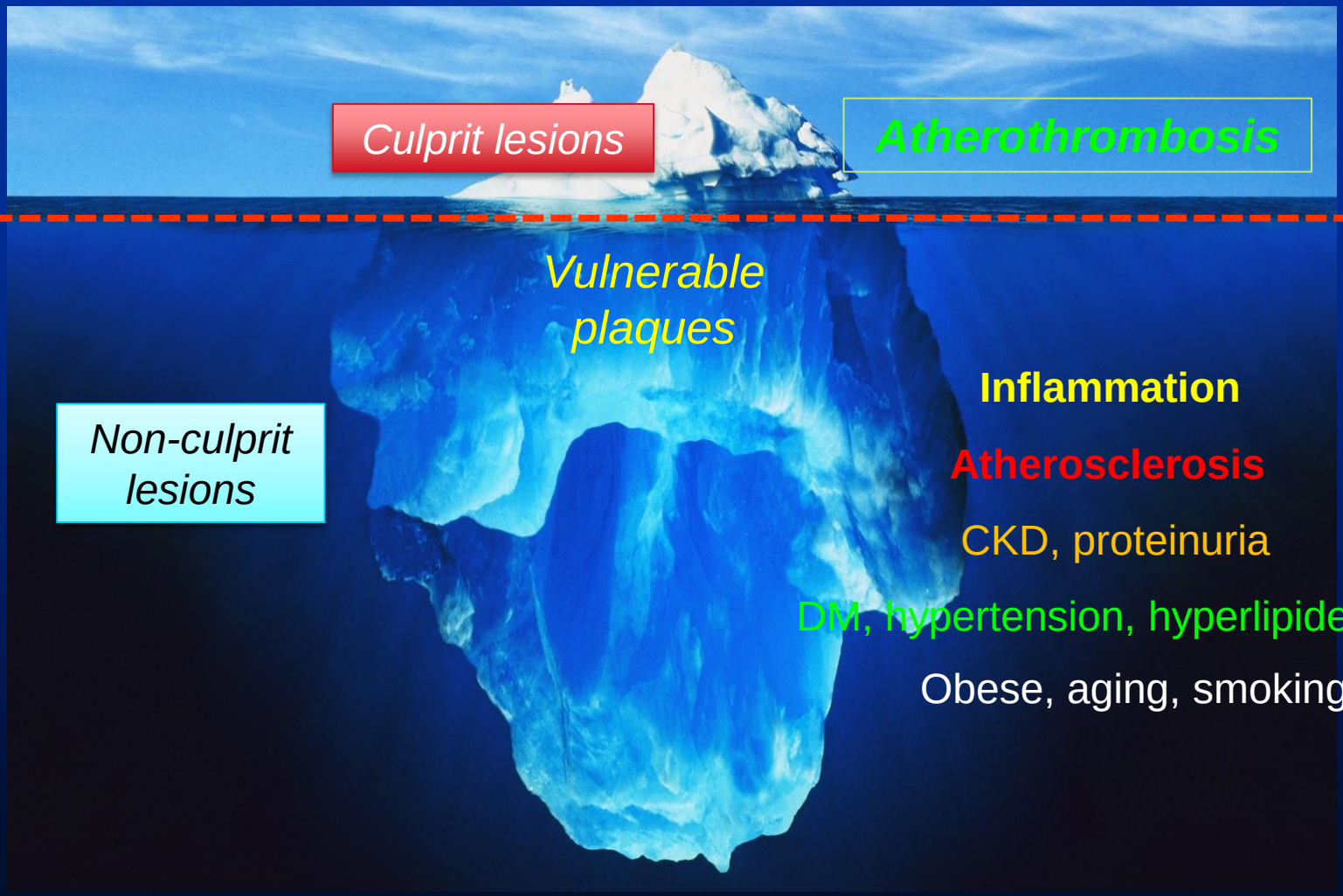
# The coronary culprit lesion is only the tip of the iceberg !!



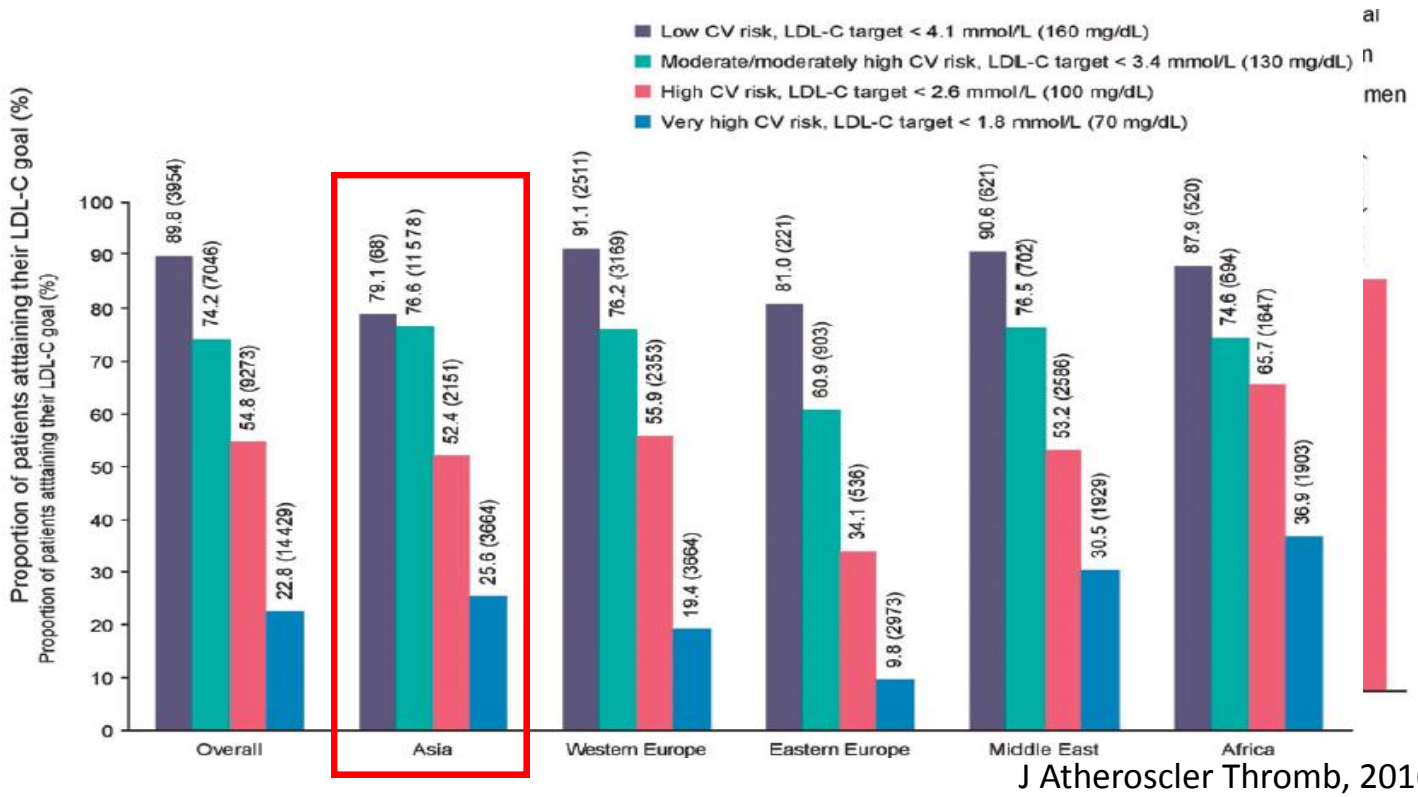
Journal of A CEPHEUS Vol.23, No.5 567

Original Article

# Suboptimal Control of Lipid Levels: Results from 29 Countries Participating in the Centralized Pan-Regional Surveys on the Undertreatment of Hypercholesterolaemia (CEPHEUS)

Chern-En Chiang[1], Jean Ferrières[2], Nina N Gotcheva[3], Frederick J Raal[4], Abdulla Shehab[5], Jidong Sung[6], Karin M Henriksson[7,8] and Michel P Hermans[9]

**only 25.6% of very high risk patients reached their recommended LDL-C level(<70mg/dL).**




J Atheroscler Thromb, 2016; 23; 567-587

# T-SPARCLE

RESEARCH ARTICLE

## Determinants for Achieving the LDL-C Target of Lipid Control for Secondary Prevention of Cardiovascular Events in Taiwan

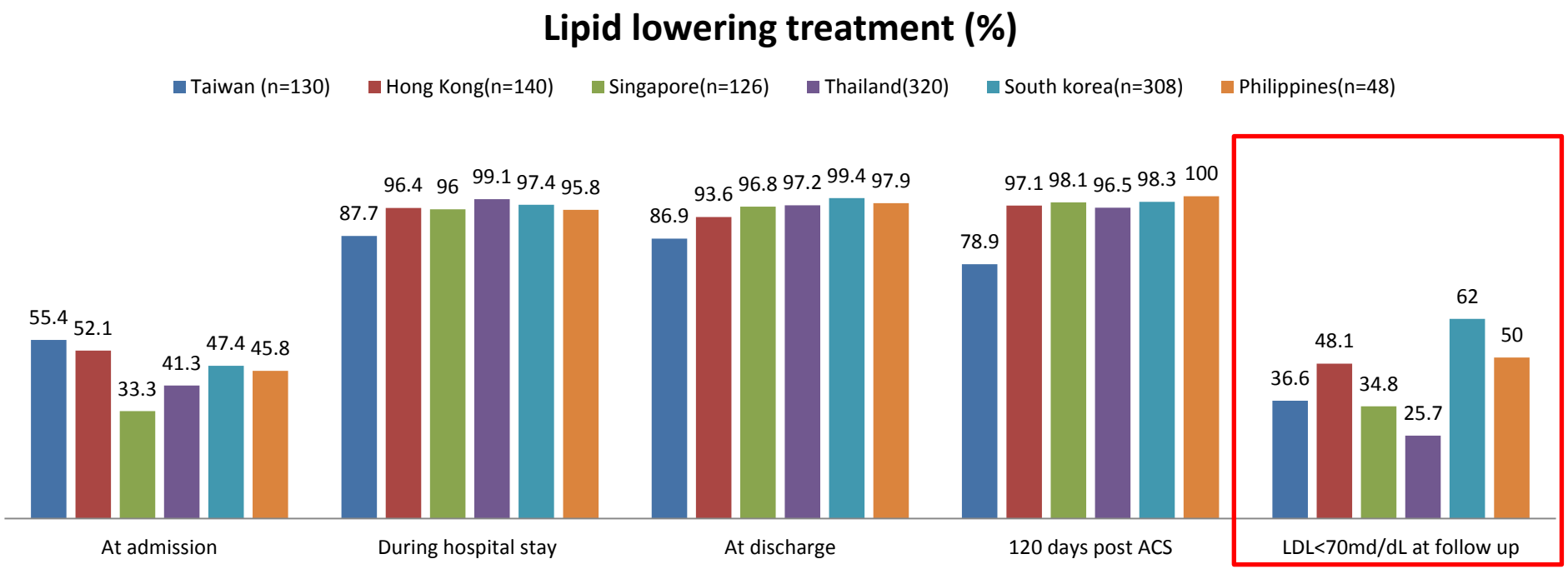
**Among the 3,486 registered patients, only 54% of the patients achieved the optimal LDL-C level (<100mg/dL); 69.1% achieved the HDL-C goal (>40mg/dL); 31.1% achieved optimal TG level (<150mg/dL)**

| Variable | N | Mean | STD |
|---|---|---|---|
| HDL-C, mg/dL | 3486 | 45.69 | 14.11 |
| Low HDL <40mg/dL, % | 1075 | 30.8% | |
| LDL-C, mg/dL | 3486 | 101.47 | 34.48 |
| High LDL-C >100mg/dL, % | 1604 | 46% | |
| TG, mg/dL | 3486 | 139.95 | 90.04 |
| High TG >200mg/dL, % | 2401 | 68.9% | |

Ho LT, Yin WH, Chuang SY, Tseng WK, Wu YW, et al. (2015) Determinants for Achieving the LDL-C Target of Lipid Control for Secondary Prevention of Cardiovascular Events in Taiwan. PLOS ONE 10(3): e0116513. https://doi.org/10.1371/journal.pone.0116513
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116513

# Only 36.6% patients in Taiwan Attained the LDL < 70%

***DYSIS II***

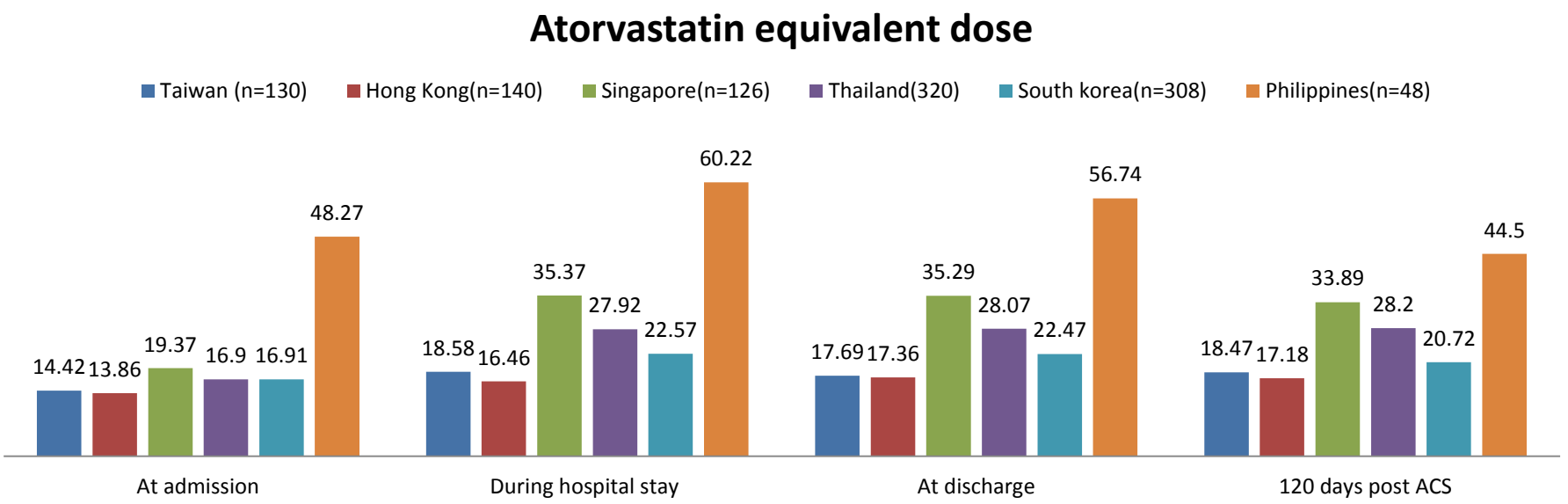


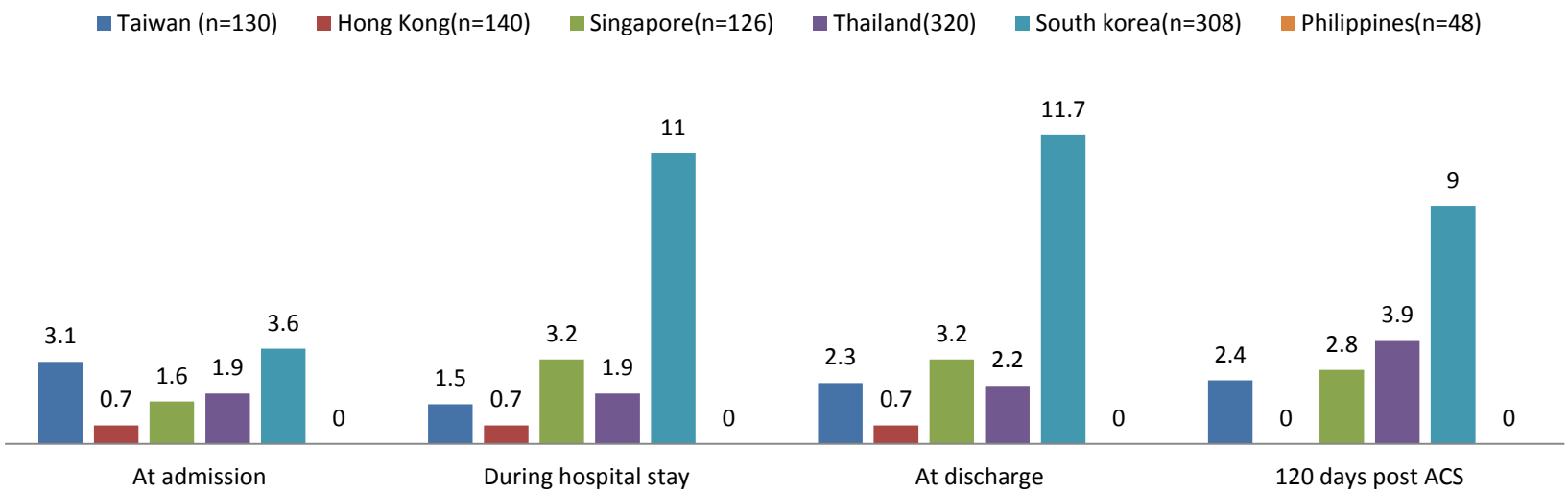

A.K.Gittetal. Data in Brief 16(2018)369–375

## ***Not attained LDL targets, why?***

- Physicians ***DO NOT*** buy in the evidence regarding LDL < 70
- No suitable medication, most standard-dose statins are not potent enough
- Patient can't tolerate high-potency statins
- Not reimbursed

# DYSIS II



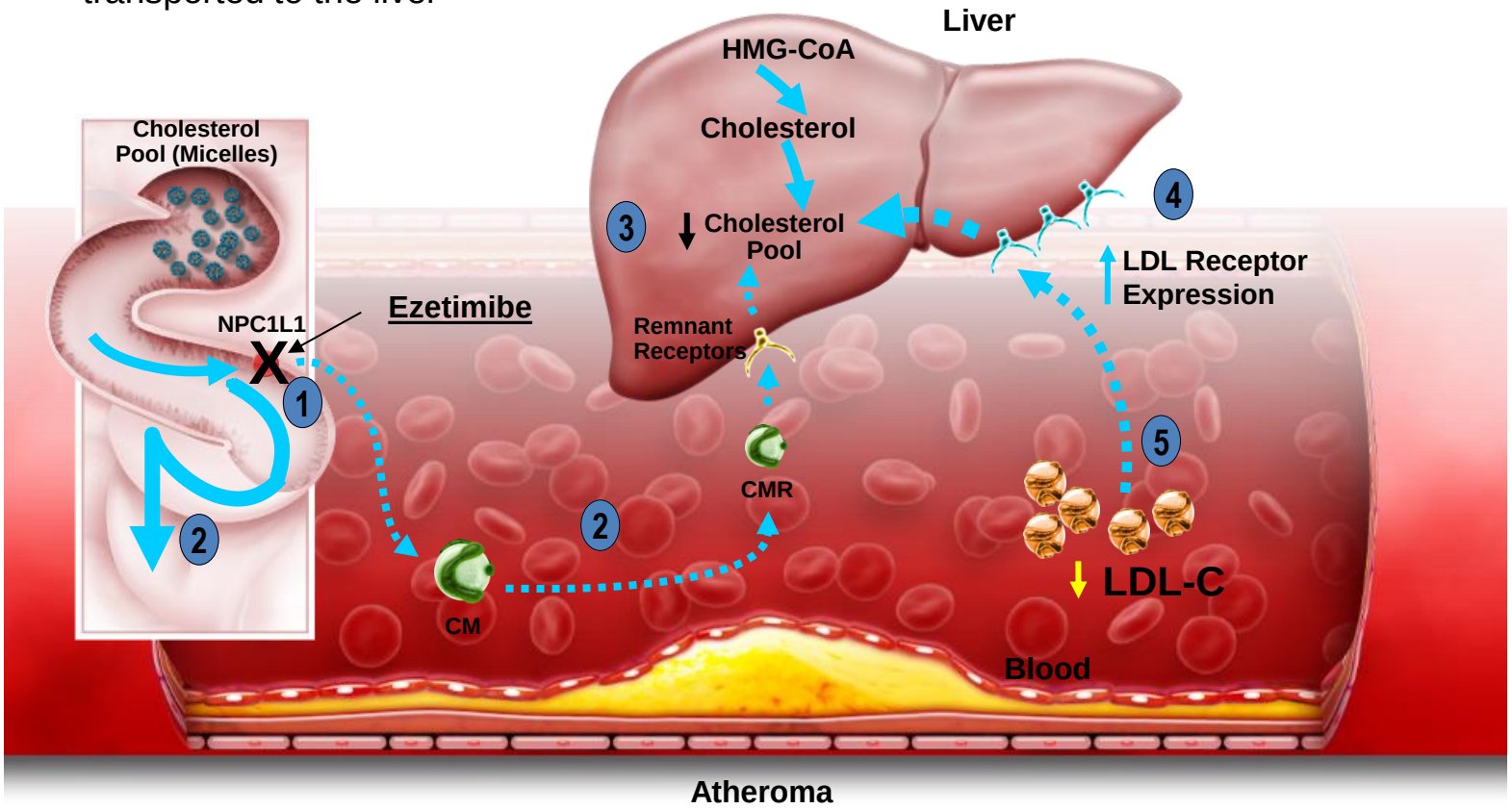




A.K.Gittetal. Data in Brief 16(2018)369–375

# Ezetimibe Inhibits Absorption of Cholesterol in the Small Intestine[1]

**Ezetimibe: Mechanism of Action**

1. Inhibition of NPC1L1 activity
2. Reduction of cholesterol transported to the liver
3. Reduction of hepatic cholesterol
4. Increased LDL receptor expression
5. Increased clearance of LDL-C

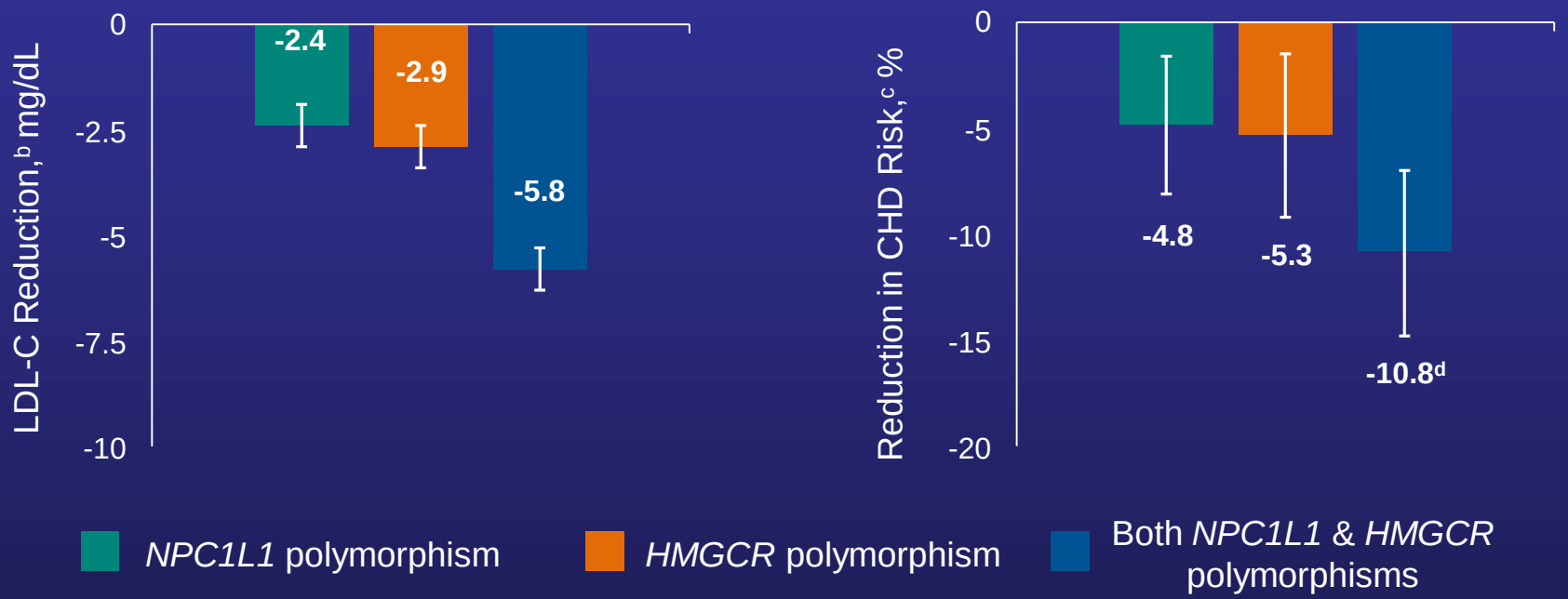



NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

**1.** Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

# Genetic Variants in NPC1L1 and HMGCR Produce Independent and Additive Reductions in LDL-C and CHD Risk

Based on a study of 108,376 subjects from 14 prospective cohort or case-control studies




[d]*P*=0.045 vs *NPC1L1* and *P*=0.021 vs *HMGCR*.

*NPC1L1* = Niemann-Pick C1-Like 1
*HMGCR* = 3 hydroxy-3-methylglutaryl-coenzyme A reductase

*Ference BA et al. J Am Coll Cardiol. 2015;65:1552–1561.*

# Study Design

IMPROVE-IT

**Patients stabilized post ACS ≤ 10 days:**
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

***N=18,144***

Standard Medical & Interventional Therapy

**Simvastatin 40 mg**

*Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)*

**Ezetimibe / Simvastatin 10 / 40 mg**

Follow-up Visit Day 30, every 4 months

*90% power to detect ~9% difference*

**Duration:** Minimum 2 ½-year follow-up **(at least 5250 events)**

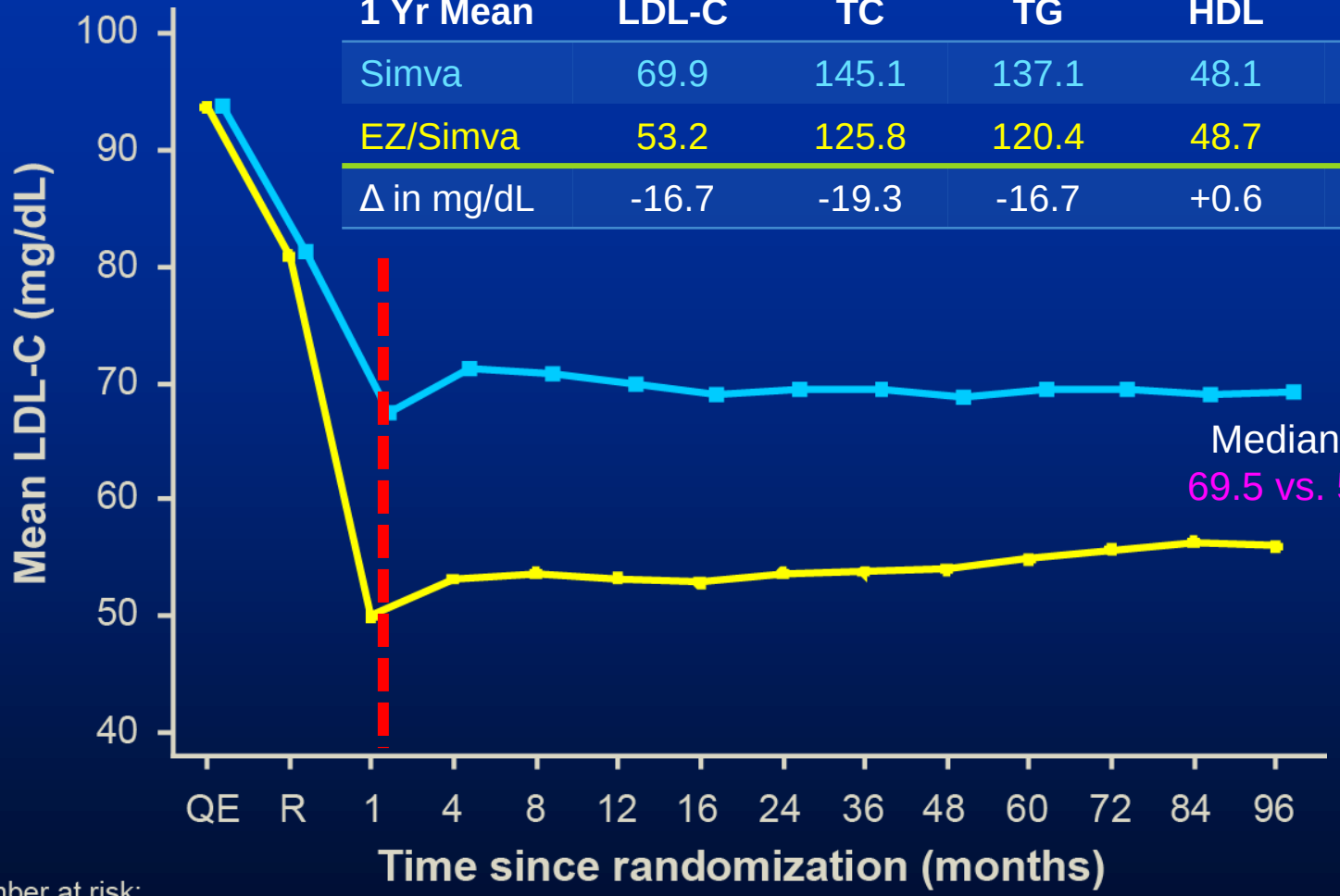
**Primary Endpoint:** CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

*Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12*

# LDL-C and Lipid Changes

IMPROVE-IT

| 1 Yr Mean | LDL-C | TC | TG | HDL | hsCRP |
|---|---|---|---|---|---|
| Simva | 69.9 | 145.1 | 137.1 | 48.1 | 3.8 |
| EZ/Simva | 53.2 | 125.8 | 120.4 | 48.7 | 3.3 |
| Δ in mg/dL | -16.7 | -19.3 | -16.7 | +0.6 | -0.5 |

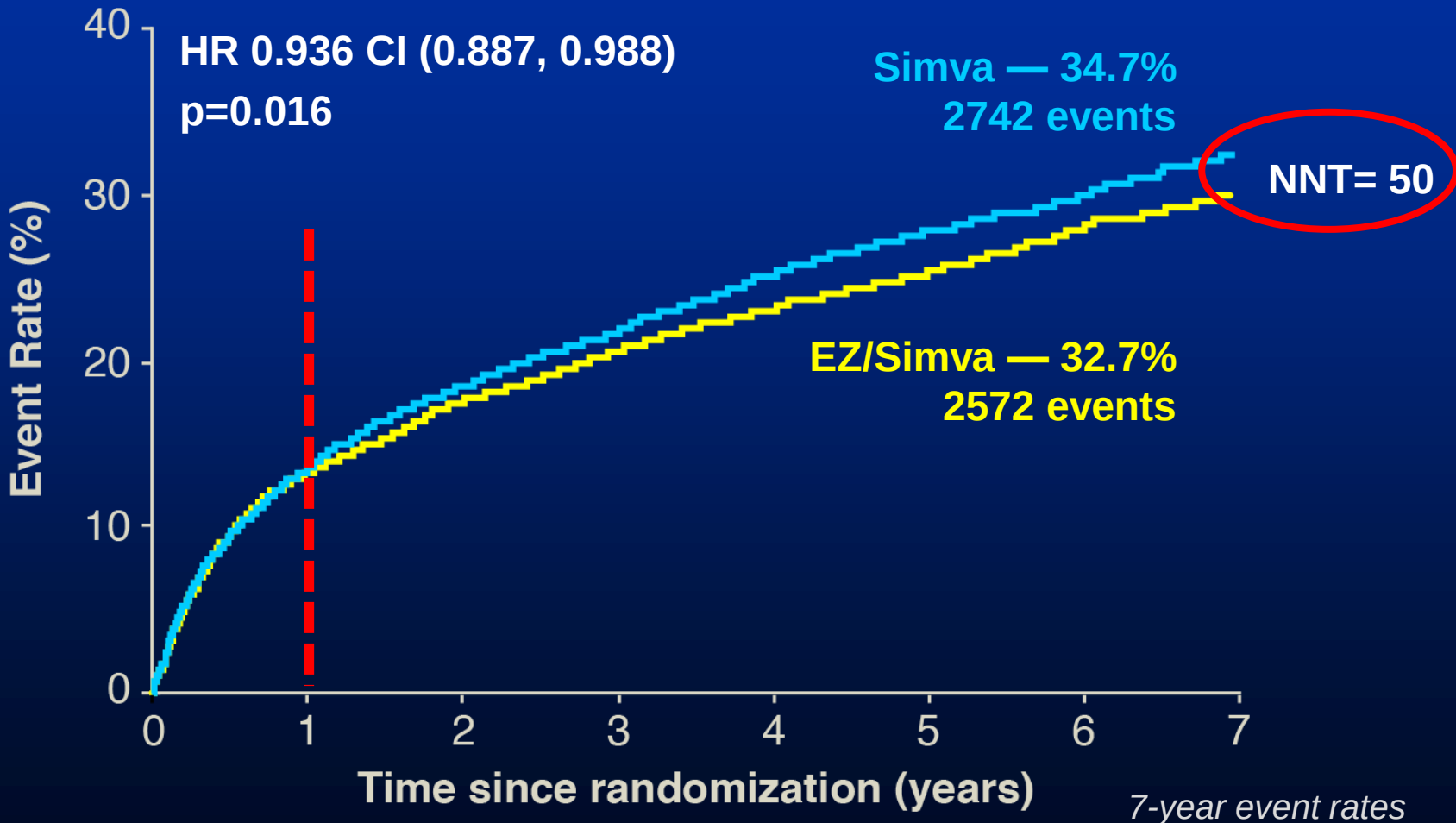



Number at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EZ/Simva | 8990 | 8889 | 8230 | 7701 | 7264 | 6864 | 6583 | 6256 | 5734 | 5354 | 4508 | 3484 | 2608 | 1078 |
| Simva | 9009 | 8921 | 8306 | 7843 | 7289 | 6939 | 6607 | 6192 | 5684 | 5267 | 4395 | 3387 | 2569 | 1068 |

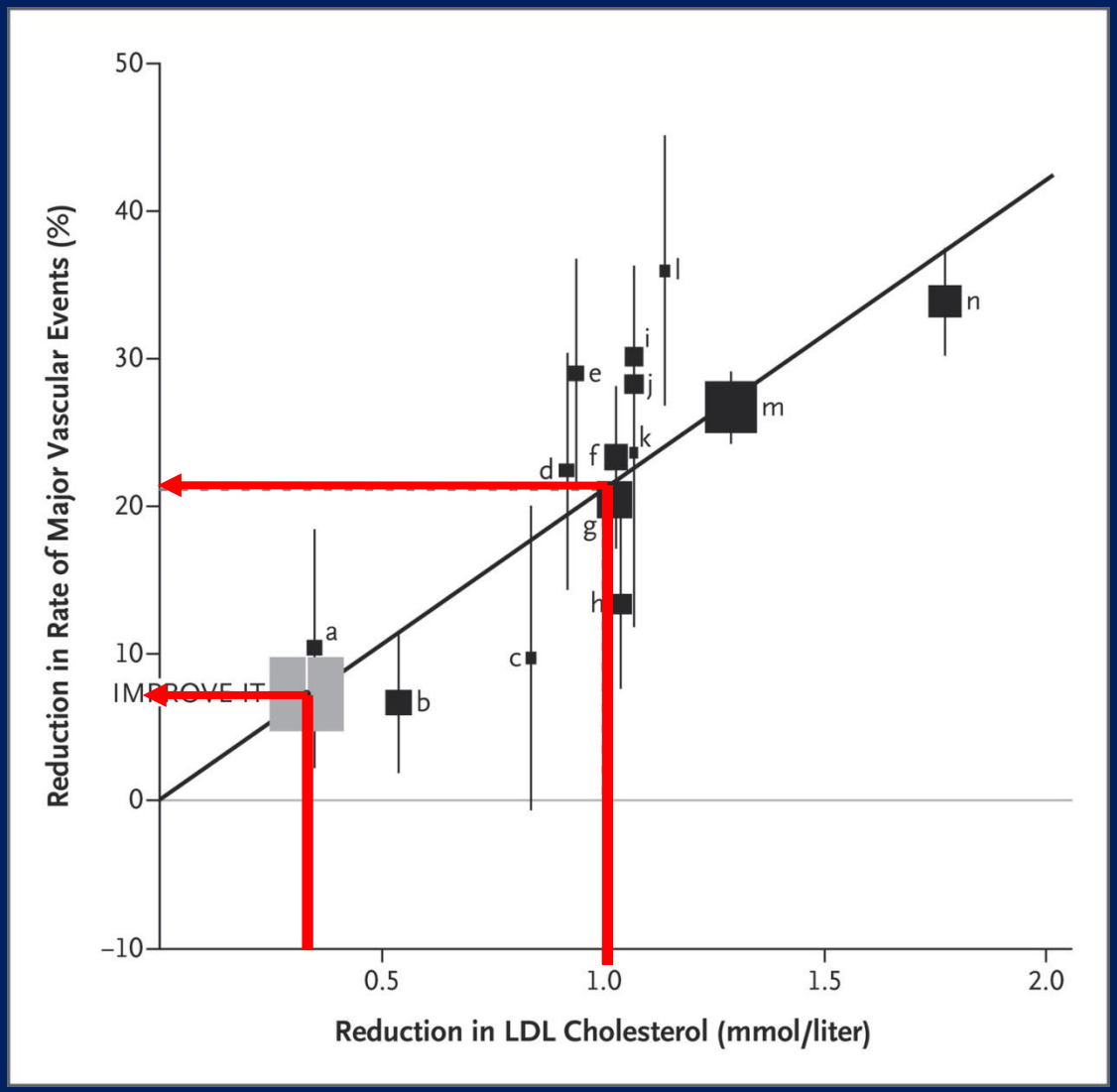
# Primary Endpoint — ITT

*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*



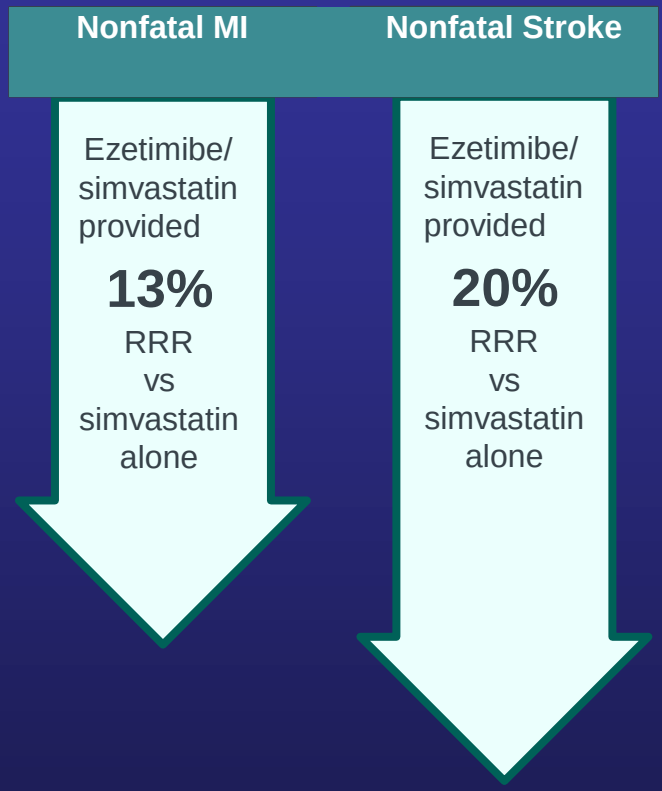

*7-year event rates*

# Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit




*Cannon CP et al. N Engl J Med 2015;372:2387-2397.*

# IMPROVE-IT: Ezetimibe/Simvastatin Reduced Nonfatal MI and Nonfatal Stroke Compared With Simvastatin Alone

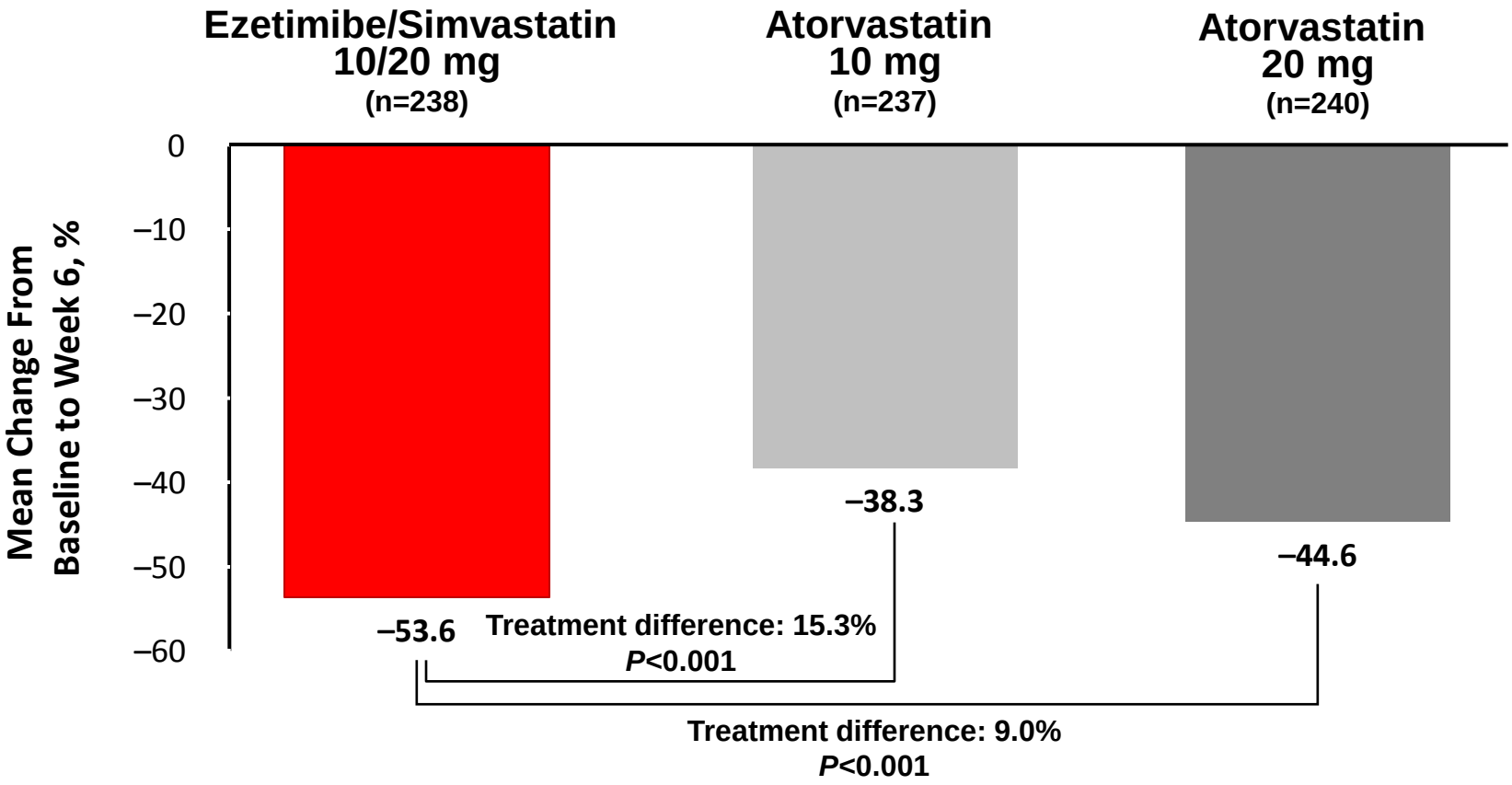



| Component of Primary End Point[a] | Ezetimibe/ Simvastatin Absolute Event Rate,[b] % | Simvastatin Absolute Event Rate,[b] % | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Nonfatal MI | 12.77 | 14.41 | 0.871 (0.798–0.950) | 0.002 |
| Nonfatal stroke | 3.49 | 4.24 | 0.802 (0.678–0.949) | 0.010 |
| Coronary revascularization ≥30 days after randomization | 21.84 | 23.36 | 0.947 (0.886–1.012) | 0.107 |
| Unstable angina requiring hospitalization | 2.06 | 1.92 | 1.059 (0.846–1.326) | 0.618 |
| CV death | 6.89 | 6.84 | 1.000 (0.887–1.127) | 0.997 |

[a]First occurrences of specified event at any time.
[b]Kaplan-Meier estimate at 7 years.

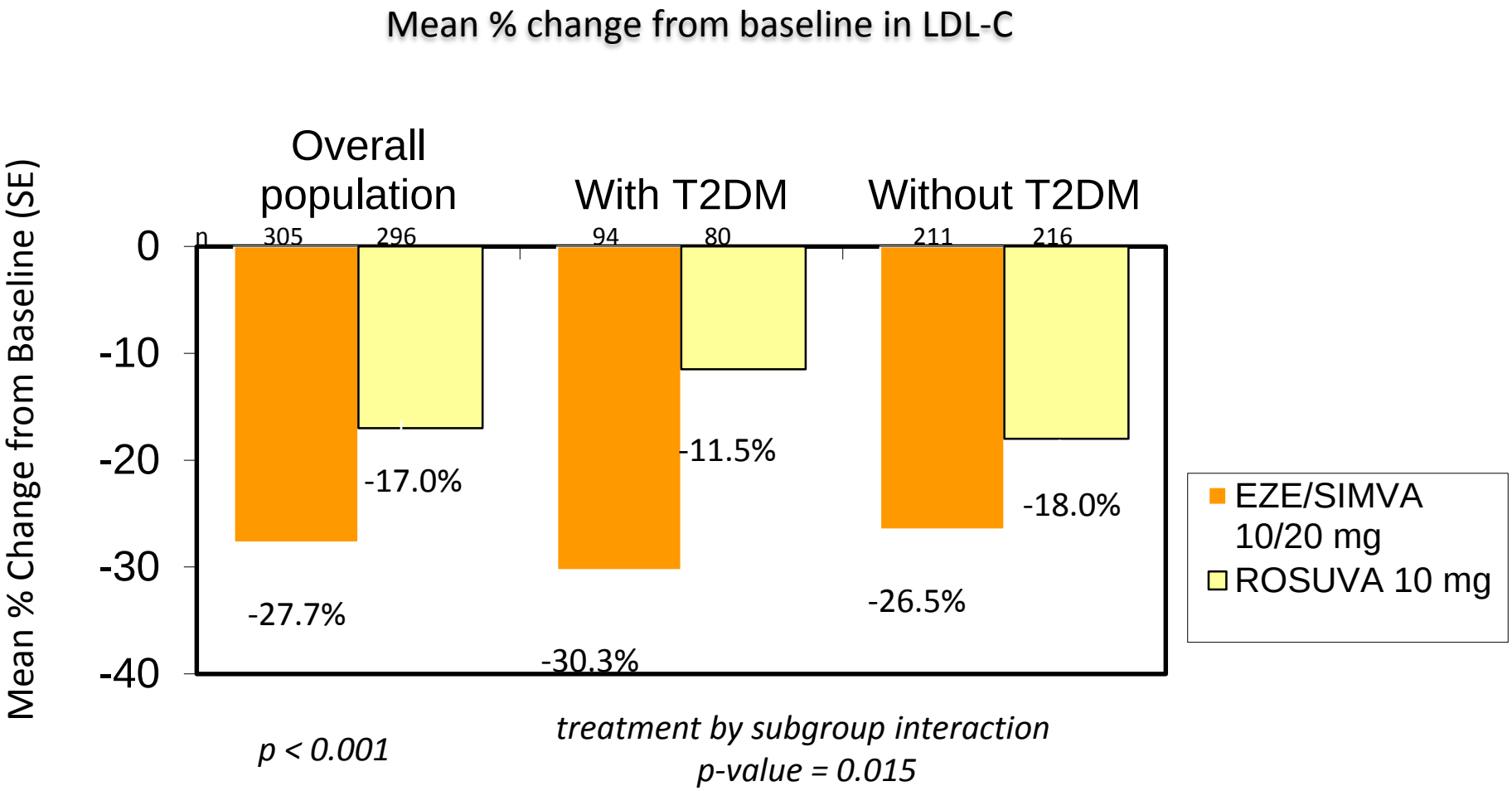
*Cannon CP et al. N Engl J Med. 2015;372:2387–2397.*

# VYTAL Study
## LDL-C Reductions: Ezetimibe/Simvastatin Superior to Atorvastatin at Usual Starting Doses in T2DM patients




Adapted from Goldberg RB, et al [published correction appears in *Mayo Clin Proc*. 2007;82:387]. *Mayo Clin Proc.* 2006;81:1579–1588.

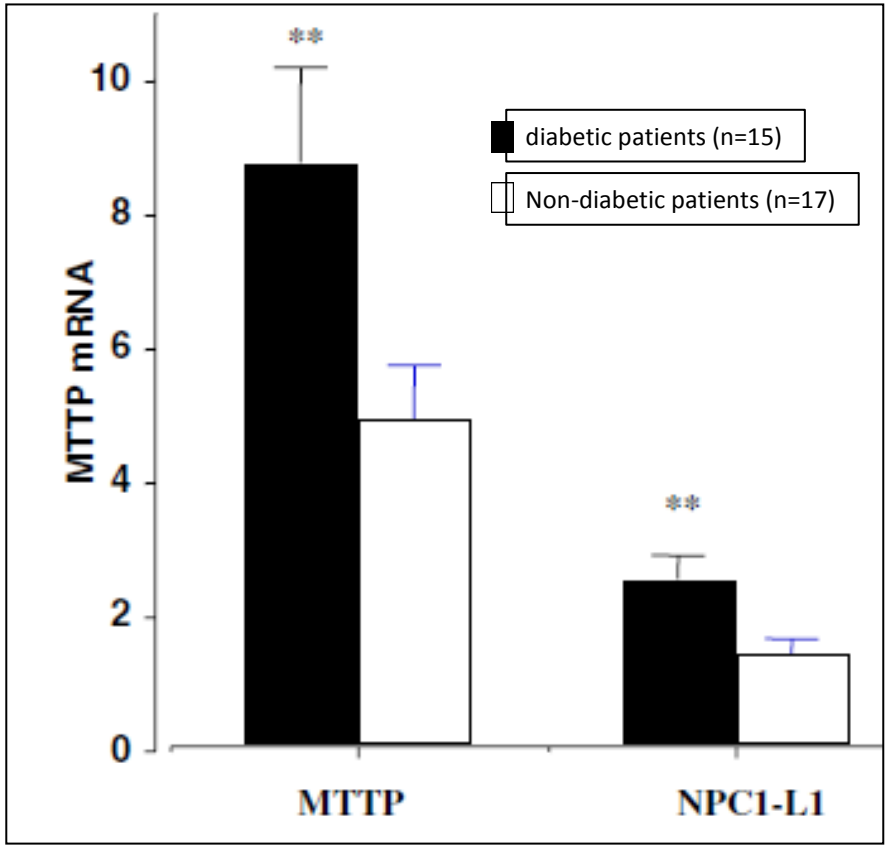
# IN-CROSS study
# Switching to Ezetimibe/Simvastatin 10/20 mg Provided Greater LDL-C Lowering vs Rosuvastatin 10 mg[1], especially in T2DM patients




1. Vaverkova et al. Cardiovasc Ther 2012, 30: 61-74

# Messenger RNA levels of genes involved in dysregulation of postprandial lipoproteins in type 2 diabetes: the role of Niemann–Pick C1-like 1, ATP-binding cassette, transporters G5 and G8, and of microsomal triglyceride transfer protein

## NPC1L1 mRNA was significantly higher in the intestine of diabetic patients than in that of control subjects




microsomal triglyceride transfer protein (MTTP)

Niemann–Pick C1-like 1 (NPC1L1)

Diabetologia (2006) 49: 1008–1016

# Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes

## IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

RP Giugliano, CP Cannon, MA Blazing, JC Nicolau,
R Corbalan, J Spinar, JG Park, JA White,
E Braunwald on behalf of the
IMPROVE-IT Investigators

CARD-1162344-0000 10/15

# Treatment Differences in Lipids and hs-CRP During the Trial

IMPROVE-IT

**Placebo-adjusted differences between treatments in the changes from baseline* to the time-weighted average during the trial†**

| Parameter | No Diabetes (ΔE/S – ΔP/S) | DM Present (ΔE/S – ΔP/S) | $P_{int}$ |
|---|---|---|---|
| **LDL-C** | **-0.37 mM/L** | **-0.43 mM/L** | **0.03** |
| Triglycerides | -0.09 mM/L | -0.13 mM/L | 0.59 |
| HDL-C | +0.013 mM/L | +0.008 mM/L | 0.30 |
| **hs-CRP*** | **-0.05 mg/L** | **-1.09 mg/L** | **0.03** |

* baseline hs-CRP at randomization; baseline lipids obtained at admission
† from month 1 to end of trial

# Individual Cardiovascular Endpoints and CVD/MI/Stroke

IMPROVE-IT

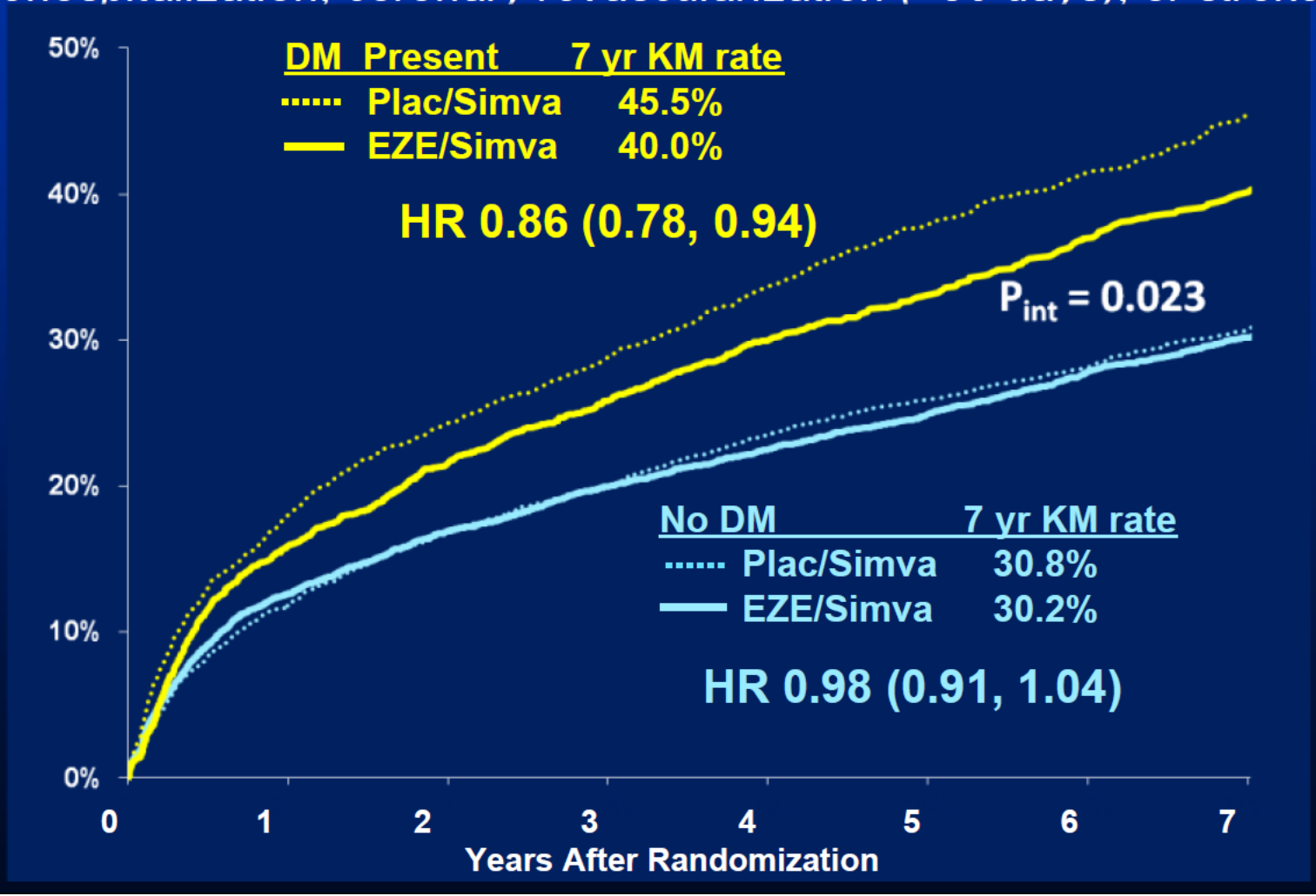
| | | HR | P/S* | E/S* | $P_{int}$ |
|---|---|---|---|---|---|
| Cardiovascular death | No DM | 1.03 | 5.3 | 5.3 | 0.57 |
| | DM | 0.96 | 11.2 | 11.7 | |
| Myocardial infarction | No DM | 0.93 | 12.7 | 12.0 | 0.028 |
| | DM | 0.76 | 20.8 | 16.4 | |
| Ischemic stroke | No DM | 0.91 | 3.4 | 3.2 | 0.031 |
| | DM | 0.61 | 6.5 | 3.8 | |
| CV death, MI, or ischemic stroke | No DM | 0.96 | 17.7 | 17.0 | 0.016 |
| | DM | 0.80 | 29.9 | 24.9 | |

*7-year event rates (%)

# Primary Endpoint — ITT

IMPROVE-IT

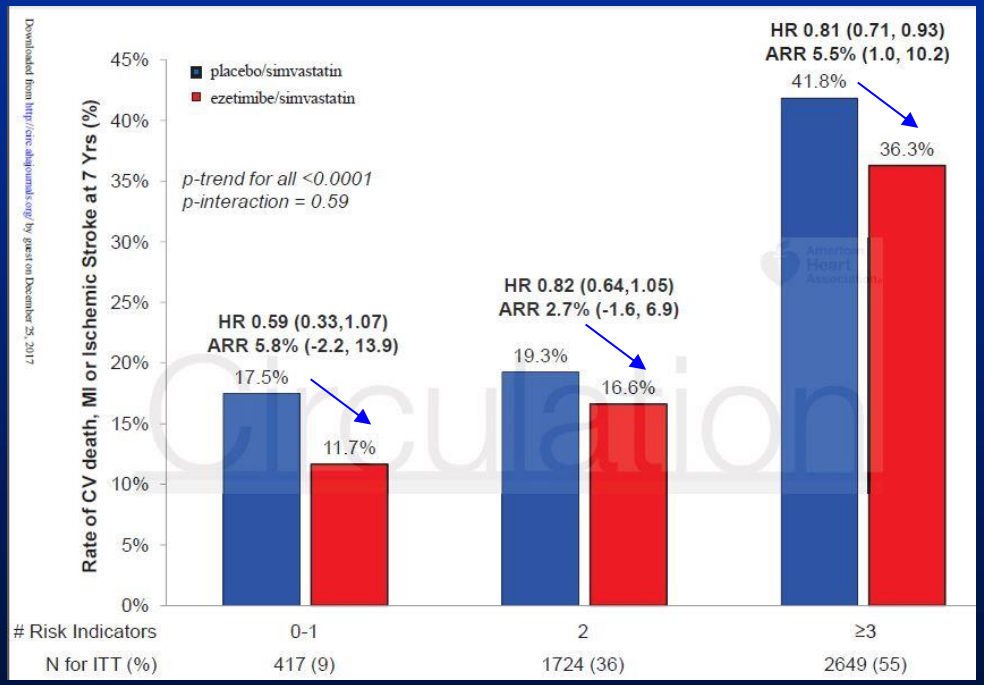
*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*



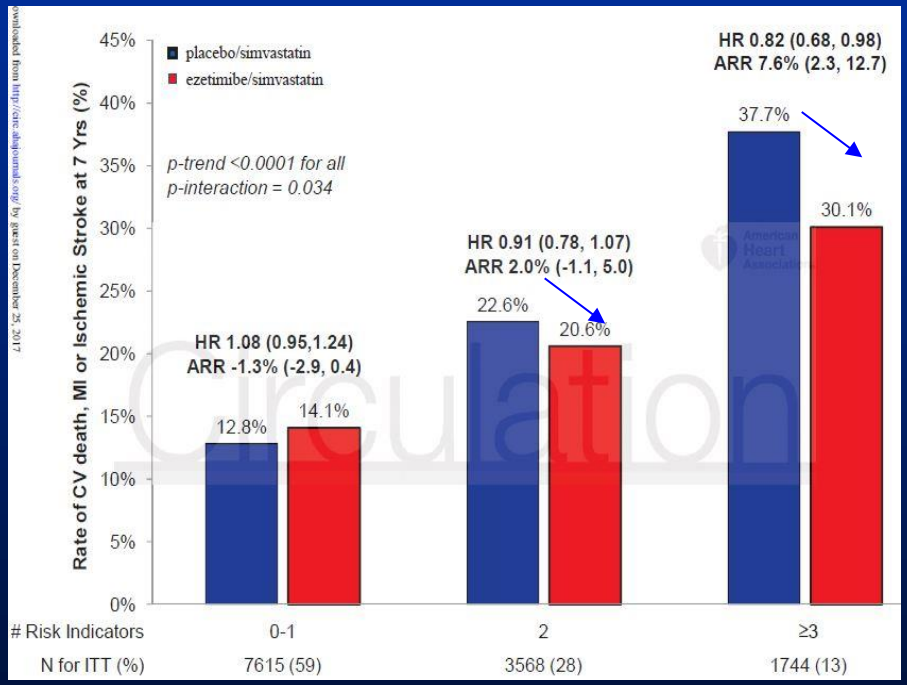
# Risk stratification and outcomes in patients with and without DM

IMPROVE-IT

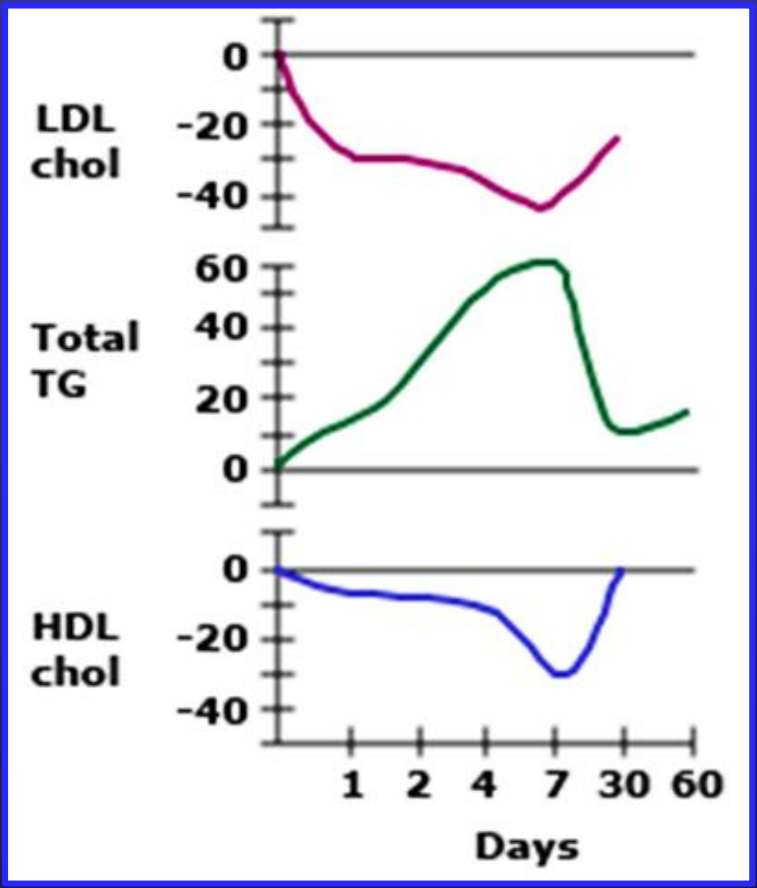
## With diabetes mellitus




## Without diabetes mellitus



# Impact on Lipid After AMI Lasted for 30 days




- HDL-C and LDL-C: decreased
- TG: elevated


- *Myocardial injury: the acute phase response and lipoprotein metabolism. J Am Coll Cardiol 1993; 22:933.*
- *Measurement of plasma lipids in patients admitted with acute myocardial infarction or unstable angina pectoris. Am J Cardiol 2001; 88:165.*

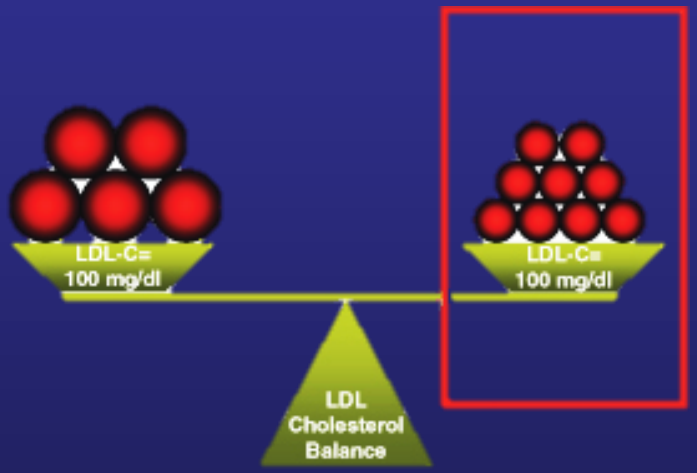
# When to Check Lipid Profiles After AMI

- Possible causes include tissue injury, which can reduce total cholesterol, HDL-C, LDL-C, and apolipoproteins B and A-I.
- Stress-induced myocardial injury has been associated with triglyceride elevation.
- Previous suggestion:
  - Obtain lipid profiles within hours, or
  - > 1 months after index ACS
- LUNAR trial enrolled 2x NSTE-ACS patients found that lipids profiles remain relatively stable for the first 96 hours after an ACS.
- Current recommendation:
  - LDL-C and HDL-C are relatively accurate when measured in the first 24 to 48 hours after STEMI and up to 96 hours after NSTEMI.
  - Non-fasting values are acceptable.


- *Lipid levels in the post-acute coronary syndrome setting: destabilizing another myth? J Am Coll Cardiol 2008; 51:1446.*
- *Lipid levels after acute coronary syndromes. J Am Coll Cardiol 2008; 51:1440.*

# Cardiovascular Risk Tracks With Particles, NOT Cholesterols

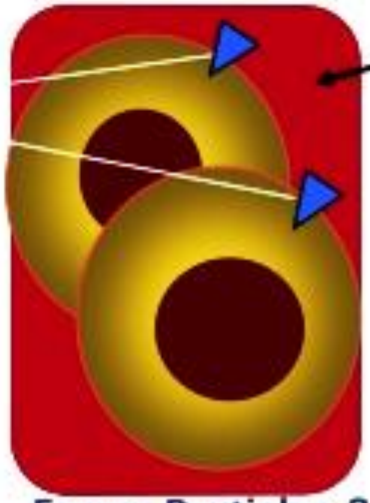
- LDL-cholesterol (LDL-C) does not accurately quantify LDL particles no matter how accurately the analytical techniques.
- This situation is most notable when the LDL particle size is small, since small LDL particles carry less cholesterol than large LDL particles.
- For the same amount of LDL-C, the patient with smaller LDL particles may require nearly 70 percent more LDL particles to carry the same amount of cholesterol as the patient with larger LDL particles.
- There are strong associations between LDL particles and cardiovascular disease.





1. *Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep 2004; 6:381.*
2. *Underappreciated opportunities for low-density lipoprotein management in patients with cardiometabolic residual risk. Atherosclerosis 2010; 213:1.*

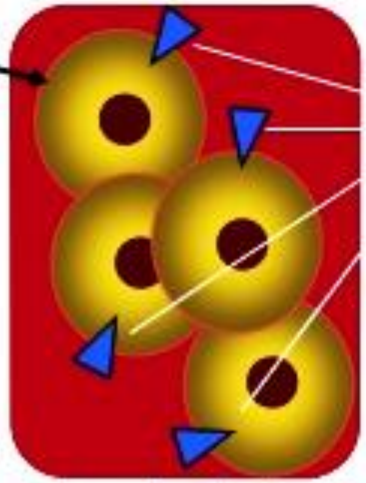
# Same LDL-C Levels, Different Cardiovascular Risk.



Large LDL

Apo B

LDL-C
130 mg/dL



Small Dense LDL

More Apo-B

Fewer Particles &
Less Risk/Particle

More Particles &
More Risk/Particle

| Lipid Profile | |
|---|---|
| TC | 198 mg/dL |
| LDL-C | 130 mg/dL |
| TG | 90 mg/dL |
| HDL-C | 50 mg/dL |
| Non–HDL-C | 148 mg/dL |

| Lipid Profile | |
|---|---|
| TC | 210 mg/dL |
| LDL-C | 130 mg/dL |
| TG | 250 mg/dL |
| HDL-C | 30 mg/dL |
| Non–HDL-C | 180 mg/dL |

Otvos J D, et al. *Am J Cardiol*. 2002;90:22i-29i.

*Further LDL Reduction By Adding PCSK-9 Inhibitors to Statins?*

The NEW ENGLAND JOURNAL of MEDICINE

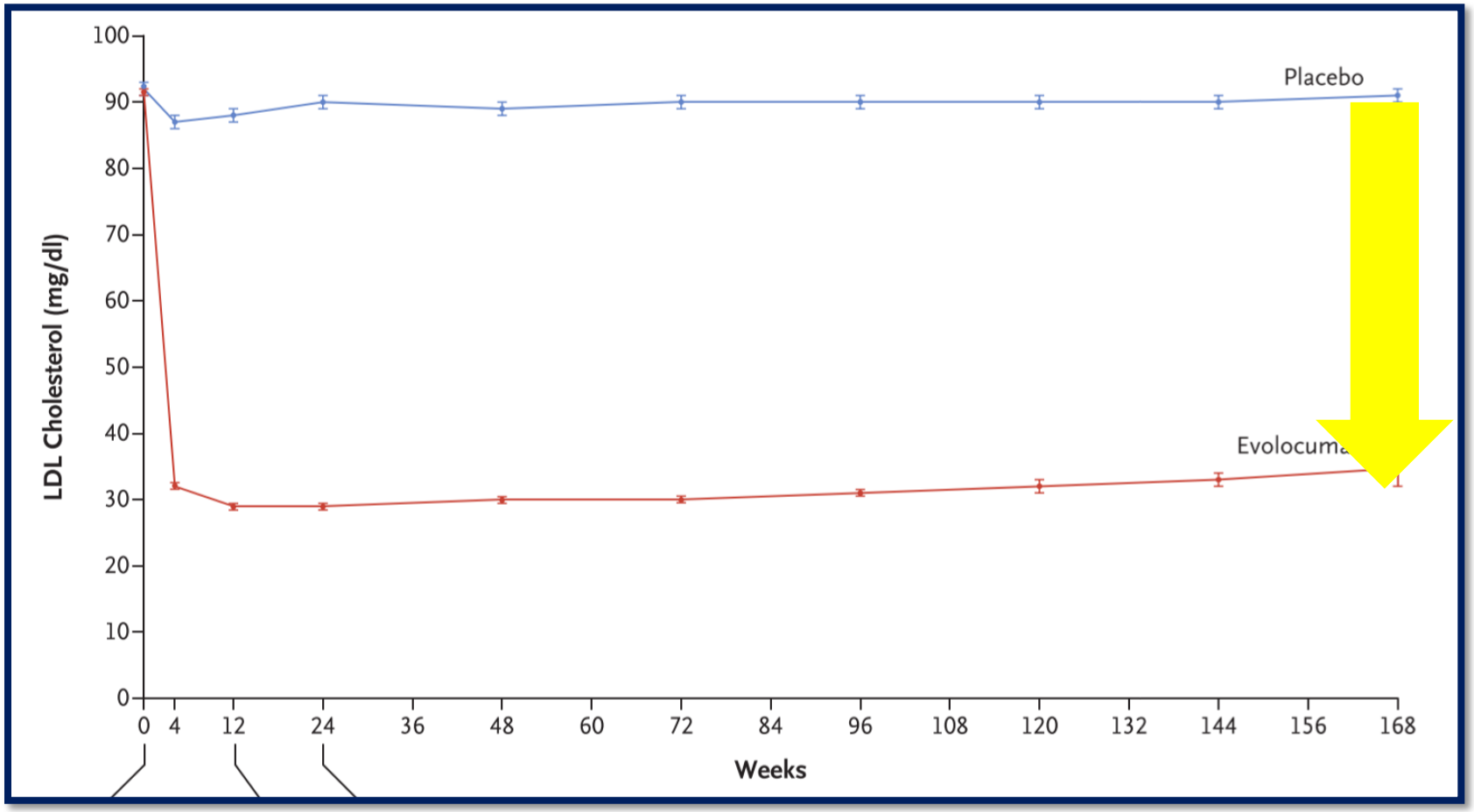
ORIGINAL ARTICLE

# Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

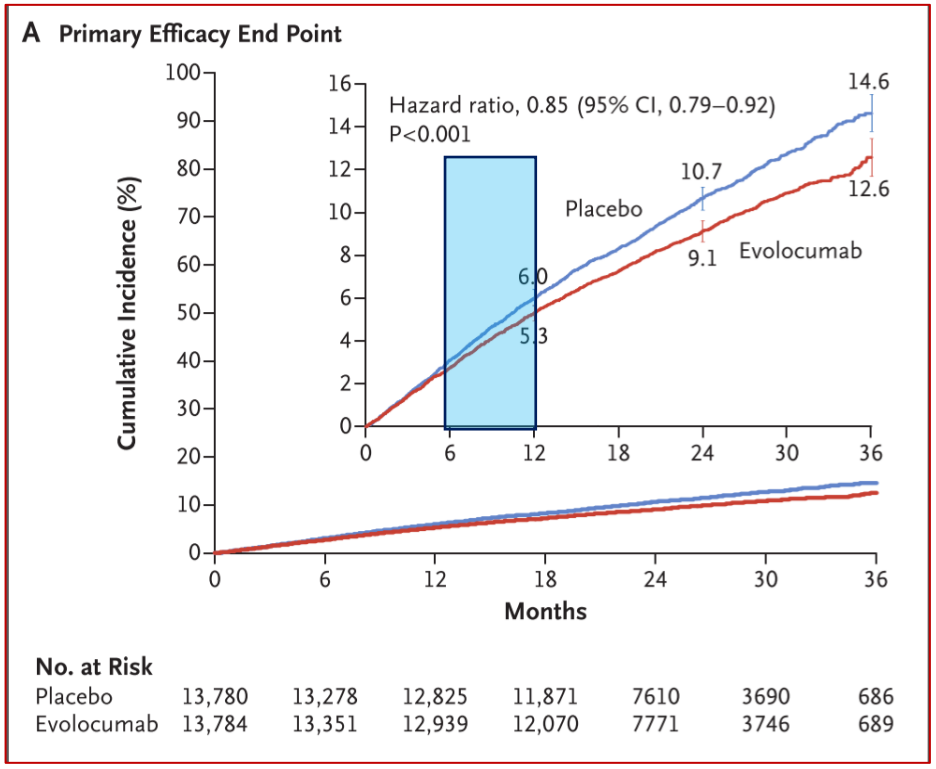
Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

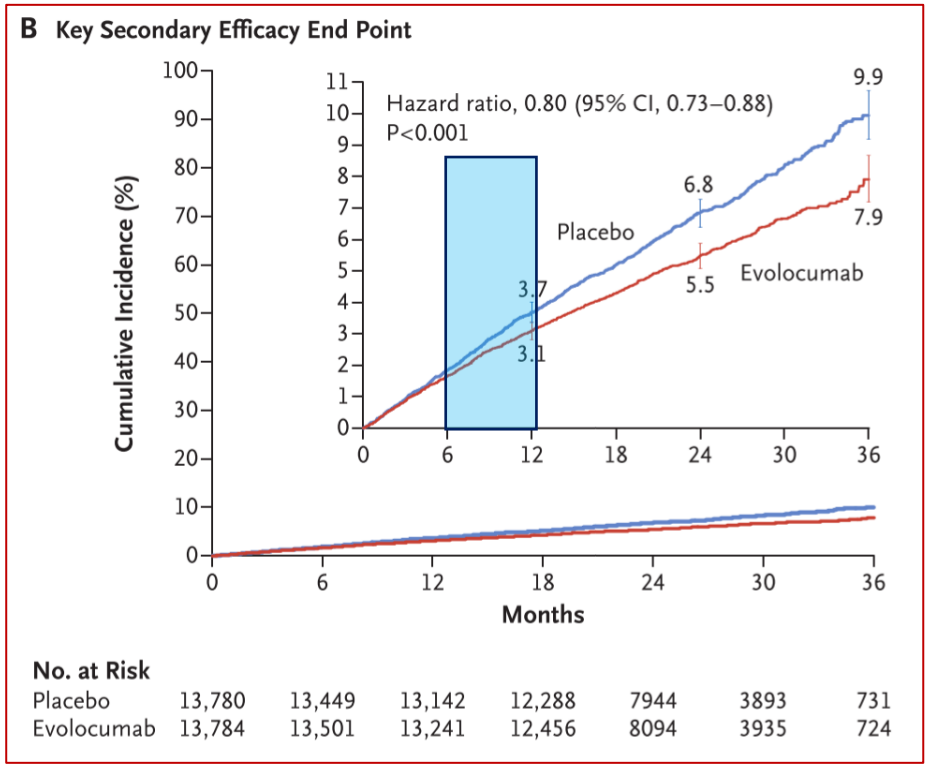
*Published on 17-March, 2017*

# Low-Density Lipoprotein (LDL) Cholesterol Levels over Time



# Cumulative Incidence of Cardiovascular Events



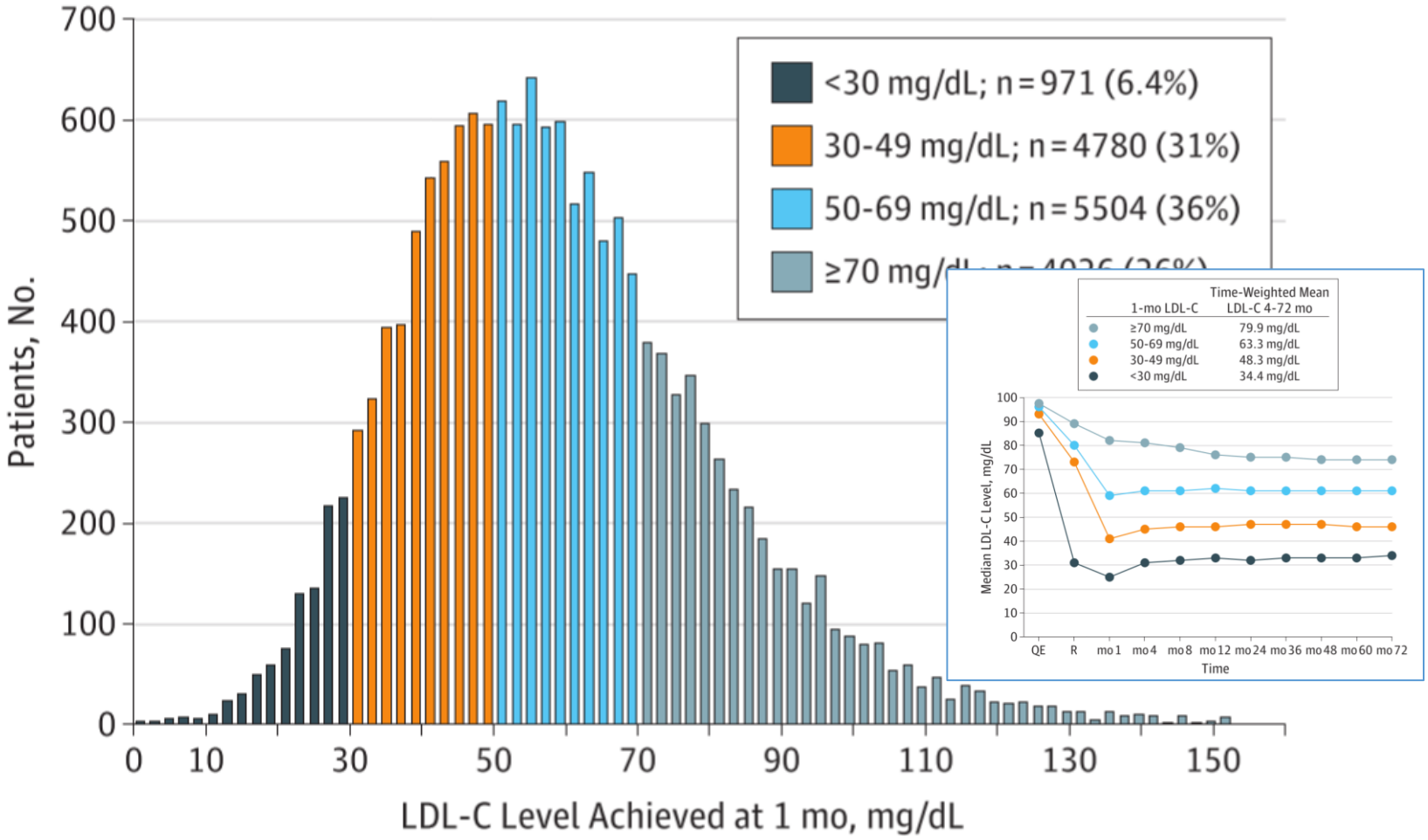



# Evolocumab Cuts the Risks of MI and Ischemic Stroke Further

| Outcome | Evolocumab (N = 13,784) | Placebo (N = 13,780) | Hazard Ratio (95% CI) | P Value* |
|---|---|---|---|---|
| | *no. of patients (%)* | | | |
| Cardiovascular death | 251 (1.8) | 240 (1.7) | 1.05 (0.88–1.25) | 0.62 |
| Due to acute myocardial infarction | 25 (0.18) | 30 (0.22) | 0.84 (0.49–1.42) | |
| Due to stroke | 31 (0.22) | 33 (0.24) | 0.94 (0.58–1.54) | |
| Other cardiovascular death | 195 (1.4) | 177 (1.3) | 1.10 (0.90–1.35) | |
| Death from any cause | 444 (3.2) | 426 (3.1) | 1.04 (0.91–1.19) | 0.54 |
| Myocardial infarction | 468 (3.4) | 639 (4.6) | 0.73 (0.65–0.82) | <0.001 |
| Hospitalization for unstable angina | 236 (1.7) | 239 (1.7) | 0.99 (0.82–1.18) | 0.89 |
| Stroke | 207 (1.5) | 262 (1.9) | 0.79 (0.66–0.95) | 0.01 |
| Ischemic | 171 (1.2) | 226 (1.6) | 0.75 (0.62–0.92) | |
| Hemorrhagic | 29 (0.21) | 25 (0.18) | 1.16 (0.68–1.98) | |
| Unknown | 13 (0.09) | 14 (0.10) | 0.93 (0.44–1.97) | |
| Coronary revascularization | 759 (5.5) | 965 (7.0) | 0.78 (0.71–0.86) | <0.001 |
| Urgent | 403 (2.9) | 547 (4.0) | 0.73 (0.64–0.83) | |
| Elective | 420 (3.0) | 504 (3.7) | 0.83 (0.73–0.95) | |
| Cardiovascular death or hospitalization for worsening heart failure | 402 (2.9) | 408 (3.0) | 0.98 (0.86–1.13) | 0.82 |
| Ischemic stroke or transient ischemic attack | 229 (1.7) | 295 (2.1) | 0.77 (0.65–0.92) | 0.003 |

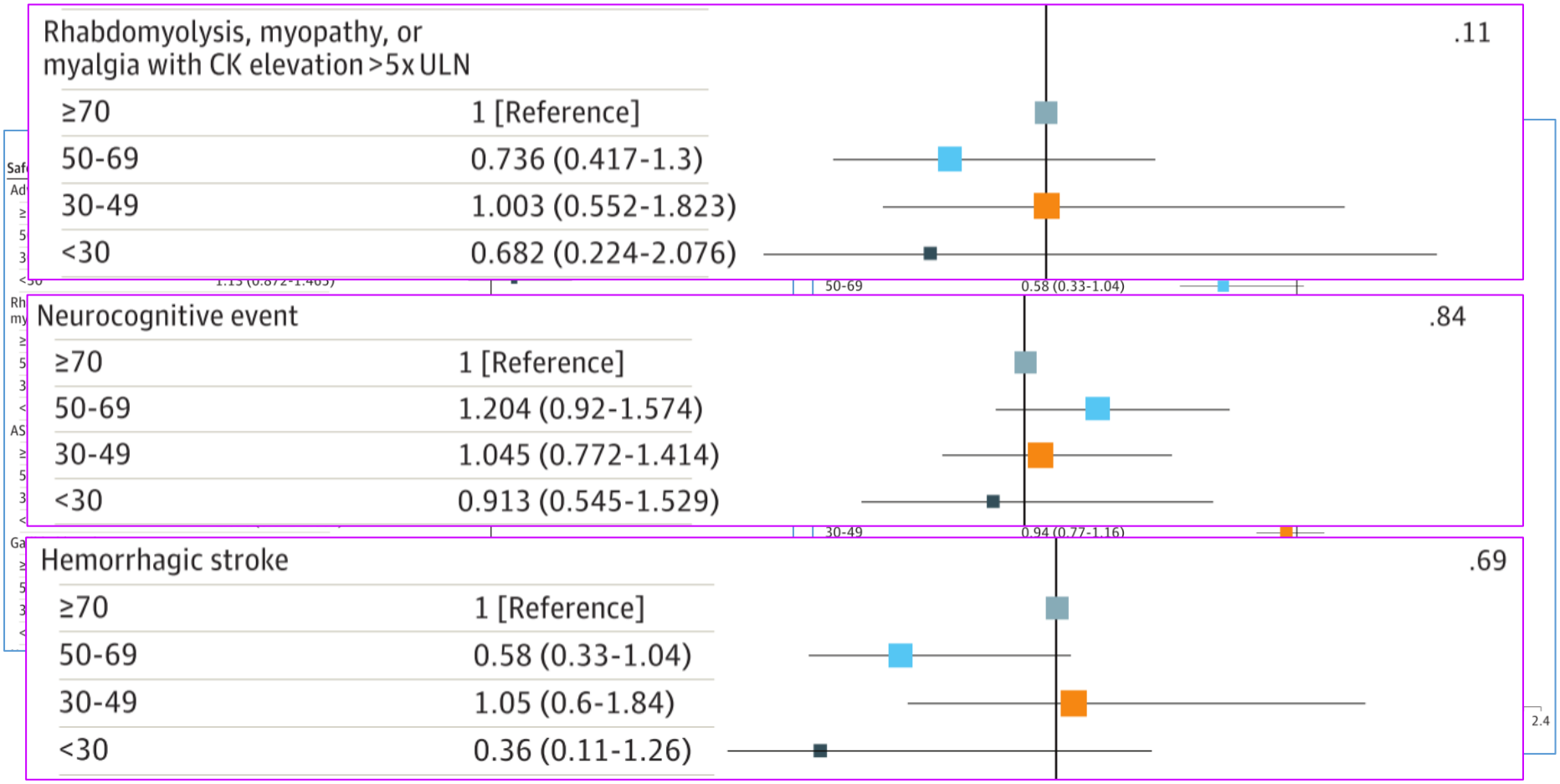
***IS Such a Low LDL Level Safe in The Long Run ?***

# IMPROVE-IT : Distribution of Achieved LDL-C at 1 Month




Giugliano R, Wiviott S, Blazing M, et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. Jama Cardiol 2017

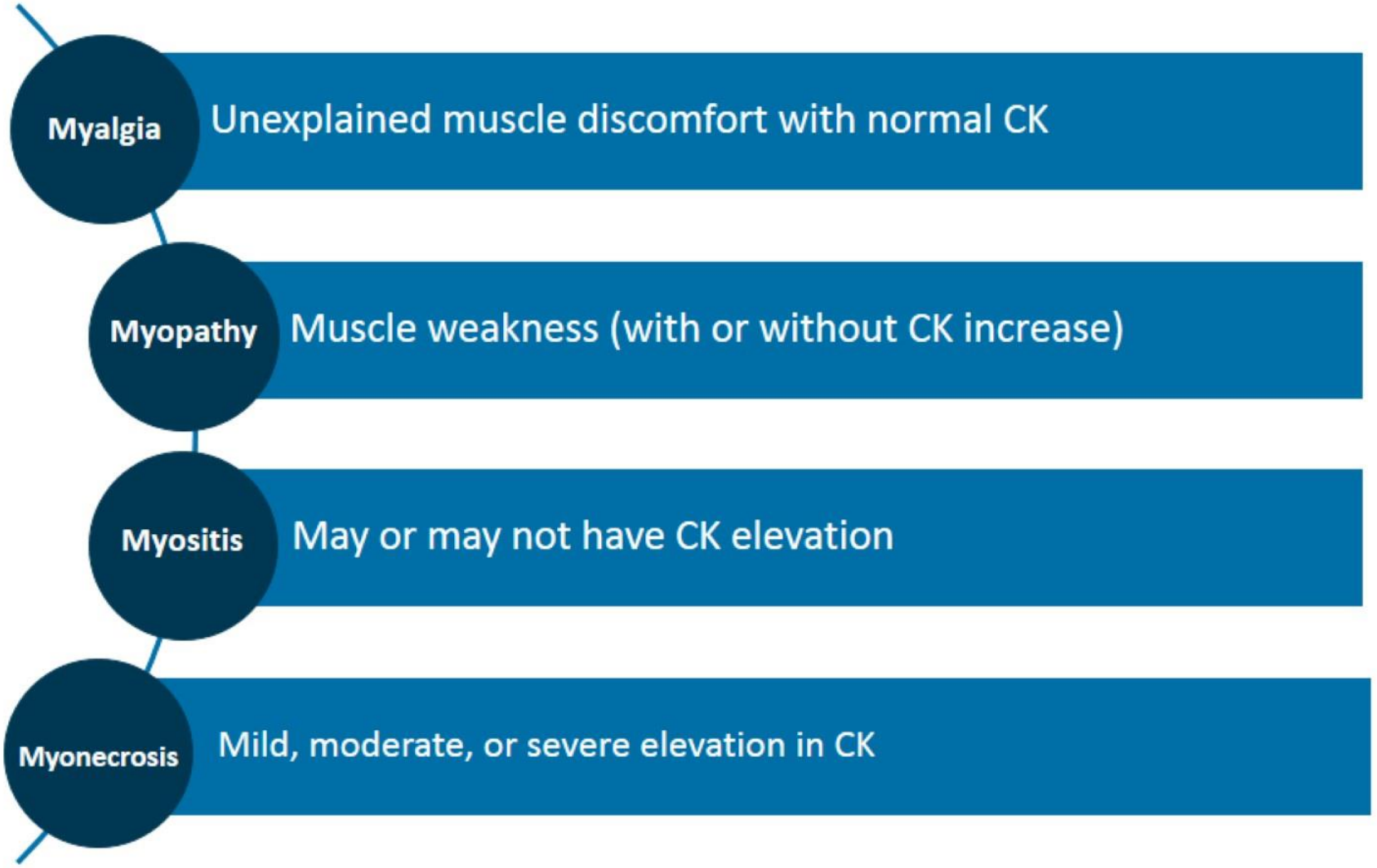
# Safety Events by Achieved LDL-C Level at 1 Month




Giugliano R, Wiviott S, Blazing M, et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. Jama Cardiol 2017

# *Statin myopathy: what should I know ?*

# Spectrum of SAMS: NLA Statin Safety Task Force




Rosenson RS. *J Clin Lipidol*. 2014;8:S58-S71.

# Clinical Features of statin myopathy

- Statin-induced myalgia and myopathy typically present as proximal, symmetric muscle weakness and/or soreness.
- There may be muscle tenderness and there may be functional impairments such as difficulty raising the arms above the head, arising from a seated position, or climbing stairs.
- These symptoms are often described as fatigue or tiredness by the patient. Less often the discomfort is asymmetric.
- Other reported symptoms include cramping (including nocturnal cramping) and tendon pain.

# Possible Confounding Conditions

- Drugs:
  - colchicine, antimalarials, cholesterol-lowering drugs (statins, gemfibrozil, nicotinic acid, and clofibrate), cocaine, and alcohol
- Disease/condition:
  - Rhabdomyolysis: trauma/injury, surgery, IM injection, EMG
  - Inflammatory/infectious/metabolic myopathies
  - Neuroleptic malignant syndrome: haloperidol
  - Malignant hyperthermia
  - Endocrine myopathies: hypothyroidism
  - Periodic paralyses: hyperthyroidism w/ abnormal K
- Exercise

# How to Manage Statin Intolerance and Recognize Risk Factors

- Nonstatin drug treatment[a]
  - Ezetimibe, bile acid resins, PCSK9 inhibitors
- Alternative dosing strategies[a]
  - Once a week (rosuvastatin)
  - 3 times a week (rosuvastatin, atorvastatin)
    - Every other day
    - Try all available statins, including:
      - » Pravastatin, luvastatin, pitavastatin
- CoQ10 not found to benefit in trials
- Vitamin D replacement (if <15 ng/mL)
- Risk factors: low BMI, female, polypharmacy, and more

Lloyd-Jones DM, et al. *J Am Coll Cardiol*. 2016;68:92-125.
JCL. 2017;in press.

# 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

**The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)**

European Heart Journal doi:10.1093 published 08/27/2016

# ESC 2016: Recommendation in ACS and PCI

| Recommendations | Class [a] | Level [b] | Ref [c] |
|---|---|---|---|
| It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values. | I | A | 64, 358–360 |
| If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients. | IIa | B | 63 |
| If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated. | IIb | C | 115, 116 |
| Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly. | IIa | C | |
| Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTE-ACS. | IIa | A | 363–365 |

*Statin pretreatment is also effective in reducing the risk of contrast-induced acute kidney injury after coronary angiography or intervention.*

# ESC 2016 Recommendation for PAD

| Recommendations | Class [a] | Level [b] | Ref [c] |
|---|---|---|---|
| PAD is a very-high-risk condition and lipid-lowering therapy (mostly statins) is recommended in these patients. | I | A | 407, 421 |
| Statin therapy should be considered to prevent the progression of abdominal aortic aneurysm. | IIa | B | 419 |

*Regarding limb prognosis, in the REACH registry, statin use was associated with an 18% lower rate of adverse limb outcomes. Even in the critical limb ischaemia, statin therapy improved rates of amputation-free survival.*

# 2016 ADA guideline on lipid management in patients with diabetes

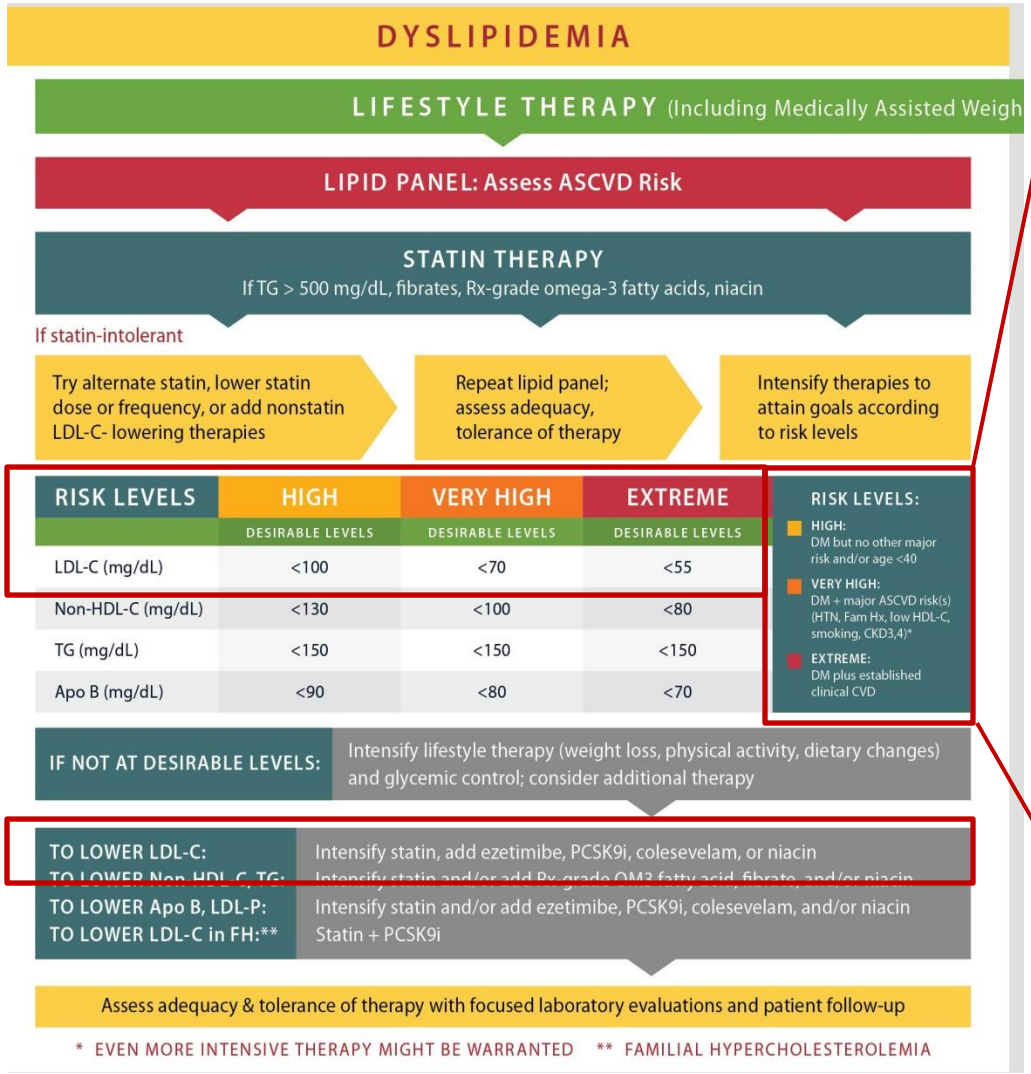
**Table 8.1—Recommendations for statin and combination treatment in people with diabetes**

| Age | Risk factors | Recommended statin intensity* |
|---|---|---|
| <40 years | None | None |
| | ASCVD risk factor(s)** | Moderate or high |
| | ASCVD | High |
| 40–75 years | None | Moderate |
| | ASCVD risk factors | High |
| | ASCVD | High |
| | ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins | Moderate plus ezetimibe |
| >75 years | None | Moderate |
| | ASCVD risk factors | Moderate or high |
| | ASCVD | High |
| | ACS and LDL cholesterol >50 mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins | Moderate plus ezetimibe |

*In addition to lifestyle therapy.
**ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

Diabetes Care 2016;39(Suppl. 1):S60–S71

# 2017 AACE & ACE Guideline




**High Risk**: DM, no other major risk & age <40
**LDL < 100 mg/dL**

**Very High Risk**: DM+ major ASCVD risk (HTN, Fam Hx, low HDL-C, Smoking, CKD 3,4)
**LDL < 70 mg/dL**

**Extreme Risk**: DM+ established clinical CVD
**LDL < 55 mg/dL**

Endocr Pract. 2016 Jan;22(1):84-113

# 2017台灣高風險病人血脂異常臨床治療指引

| 疾病 / 狀態 | 低密度膽固醇 (LDL-C) 之目標 |
| --- | --- |
| 急性冠心症候群 | < 70 mg/dL |
| 急性冠心症候群+ 糖尿病 | < 55 mg/dL 可以考慮 |
| 穩定冠狀動脈疾病 | < 70 mg/dL |
| 缺血性腦中風或暫時性腦部缺氧 | < 100 mg/dL |
| 糖尿病 | < 100 mg/dL |
| 糖尿病+心血管疾病 | < 70 mg/dL |
| 慢性腎臟病(階段 3a–5, eGFR < 60) | > 100 mg/dL 時開始治療 |
| 家族性高膽固醇血症 | 成人: < 100 mg/dL<br>小孩: < 135 mg/dL<br>有心血管疾病: < 70 mg/dL |

# Take Home Messages

- From the results of IMPROVE-IT and FOURIER Trial, CV outcome benefits comes from LDL reduction not only from statin therapy but also ezetimibe and PCSK9 inhibitors.
- Among ACS patients, those who comorbid with DM, high IHD risks and s/p CABG  benefit more from intensive Rx from simva/eze.
- Very low level LDL achieved by simva/eze had no evident signals of adverse events after long-term use.
- The LDL targets for very high/high CV risks aren't satisfied mostly even using high-dose statins, combination of statins/ezetimibe should be considered more frequently.

*Thanks for your attention !!*