# HYPERCHOLESTEROLAEMIA STATIN AND BEYOND …

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HA Convention
4 May 2016

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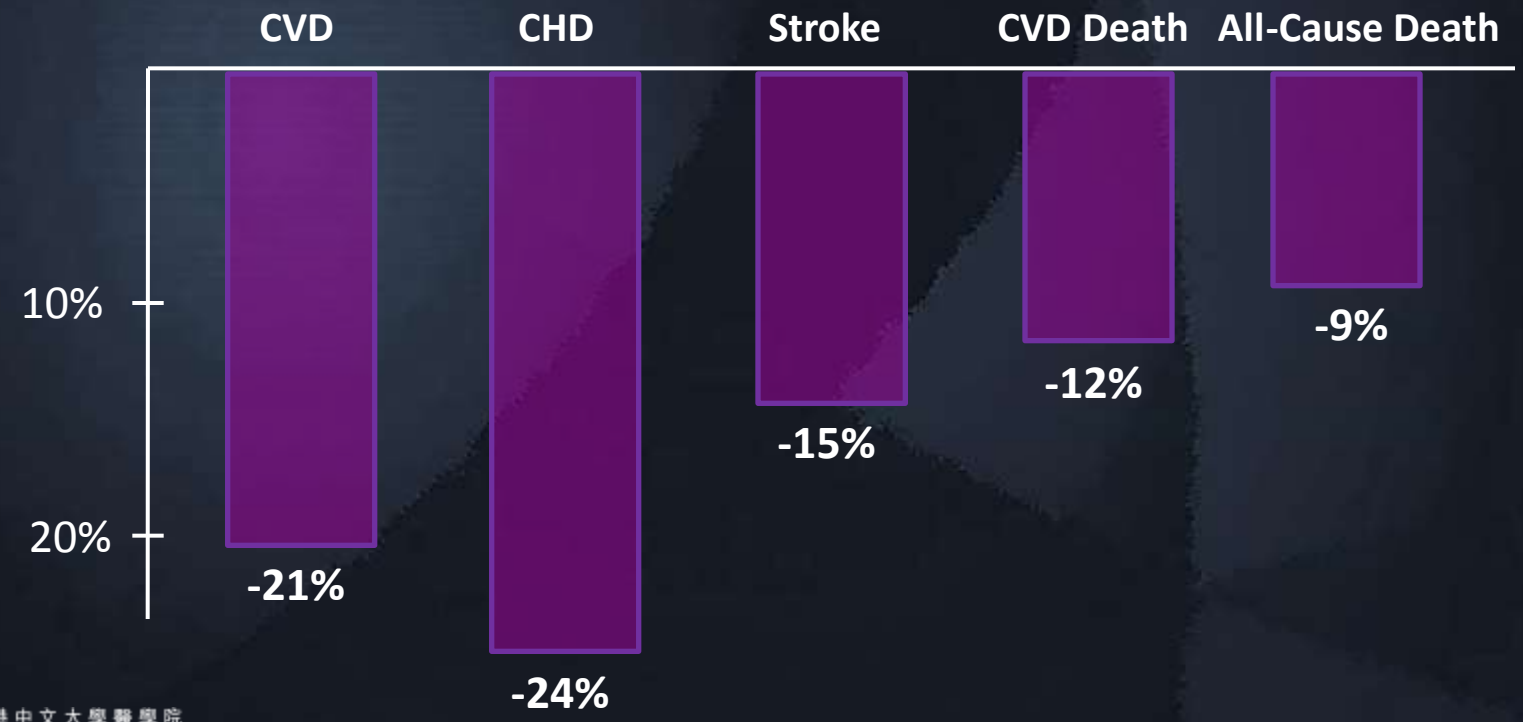
# Statins reduce CVD and all-cause mortality

**Cholesterol Treatment Trialists' Collaboration**

Meta-analysis of 27 RCT (n=174,149) comparing statin vs. placebo or high vs. low dose statins

***Relative risk reduction in major events per 1.0 mmol/L reduction in LDL-cholesterol***

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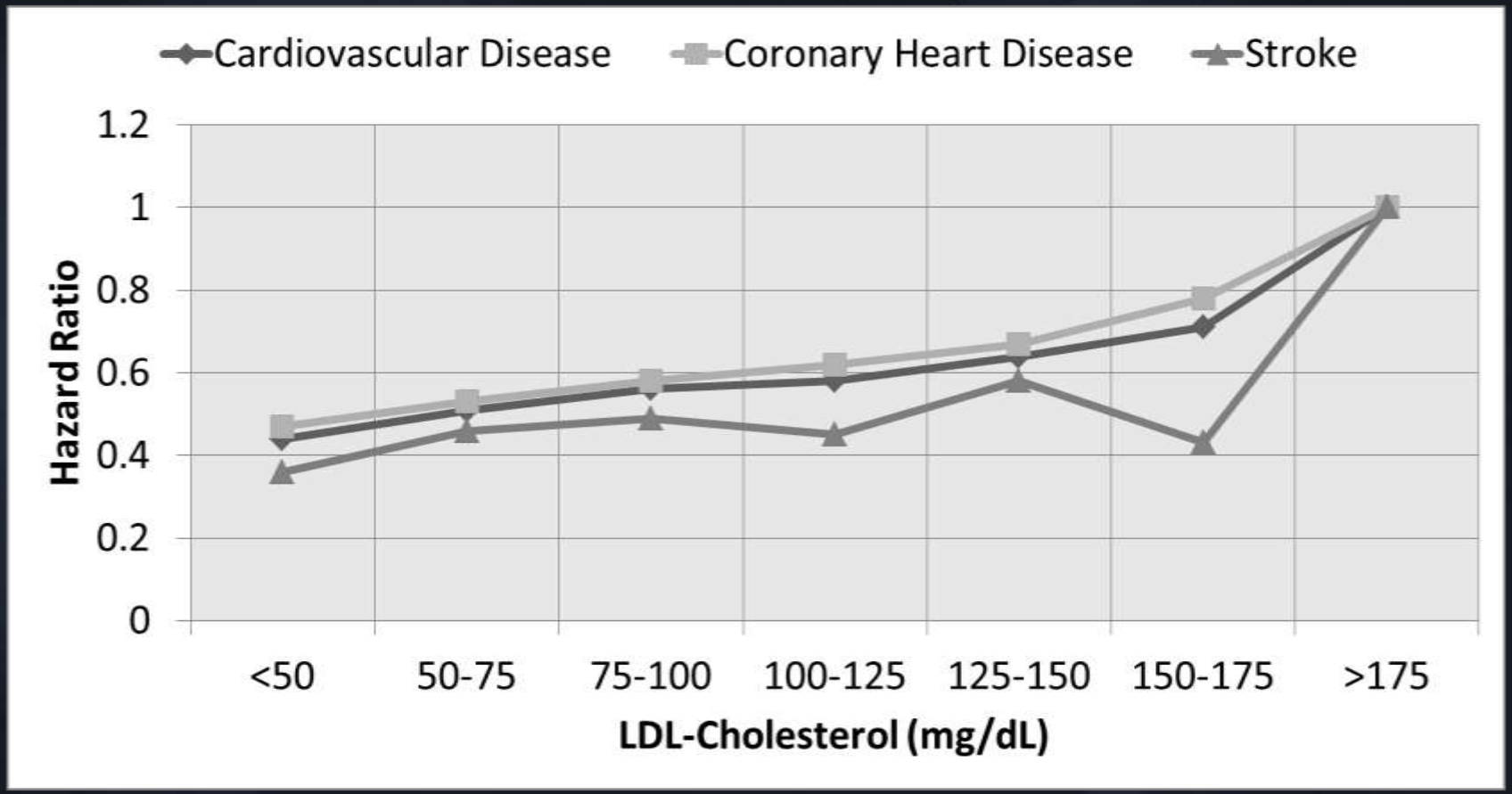
*CTT Collaboration. Lancet 2015*

# Cardiovascular benefits persist into very low levels of LDL-cholesterol






*Boekholdt SM et al. J Am Coll Cardio 2014*

# Alice in Lipidland

## The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol*

In Lewis Carroll's Alice in Wonderland, the Cheshire Cat said, "only a few find the way, some don't recognize it when they do, some ... don't ever want to."

***Wenger NK. J Am Coll Cardiol 2014***

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# 2013 ACC/AHA guideline on treatment of blood cholesterol

| | CATEGORY | STATIN THERAPY |
|---|---|---|
| 1. | Clinical ASCVD | High intensity statins if age ≤75 years<br>Mod intensity statins if age >75 years |
| 2. | LDL-C ≥4.9mmol/L* | High intensity statins |
| 3. | T2D aged 40-75 years | High intensity statins if 10-year ASCVD risk ≥7.5%<br>Mod intensity statins if 10-year ASCVD risk <7.5% |
| 4. | LDL-C 1.8-<4.9mmol/L, 10-year ASCVD risk ≥7.5% and age 40-75 years | Mod-high intensity statins if 10-year ASCVD risk ≥7.5% |

ASCVD, atherosclerotic cardiovascular disease

* Exclude secondary causes include hypothyroidism, alcoholism, nephrotic syndrome, drugs, etc



*Stone NJ et al. Circulation 2013*

# 2013 ACC/AHA cholesterol treatment guideline: Areas of controversy

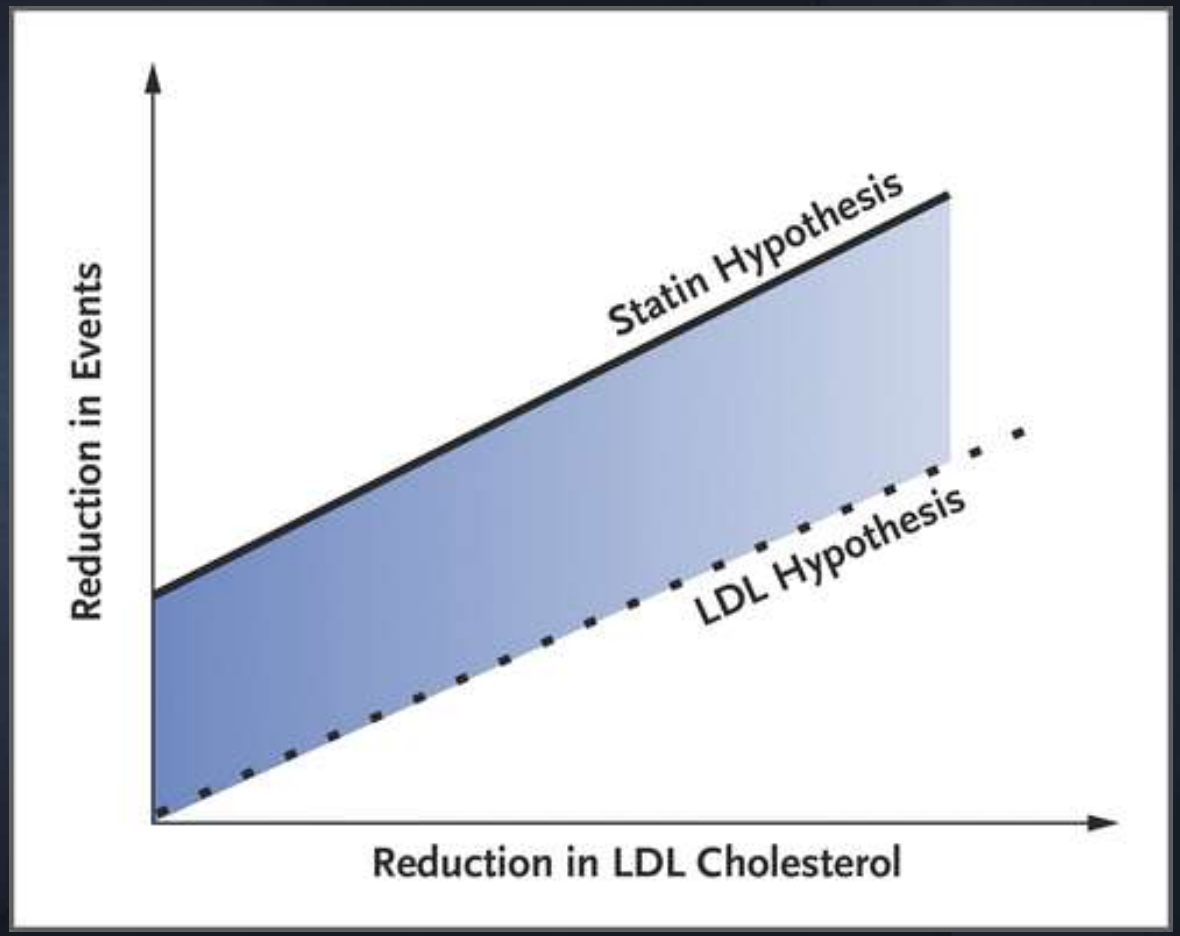
1. Certain patient groups are not addressed.
   - Patients <40 years with diabetes or high ASCVD risk.
   - Patients >75 years with diabetes or high ASCVD risk.
2. Recommended risk equations to estimate ASCVD risk not applicable to non-white, non-American black ethnicities.
3. Remove the use of LDL-C target.
4. No recommendation for use of non-statin lipid lowering drugs in patients with poor response to statin.

# U.K. National Institute for Health and Care Excellence (NICE) Guideline 2014

| | PATIENT CATEGORY | STATIN THERAPY |
|---|---|---|
| | **Secondary prevention** | Atorvastatin 80mg daily |
| | Patients with established CVD | |
| | **Primary prevention** | Atorvastatin 20mg daily |
| 1. | Type 1 diabetes if age >40 years, diabetes >10 years, established DKD, other CVD risk factors | |
| 2. | Type 2 diabetes and ≥10% 10-year risk of CVD based on QRISK2 | |
| 3. | Chronic kidney disease (GFR<60 ml/min/1.73m$^2$) | |
| 4. | ≥10% 10-year risk of CVD based on QRISK2 | |
| 5. | ≥85 years old | |

| MONITORING |
|---|
| Aim for 40% reduction in non-HDL cholesterol<br>Stepping up statin dose if this is not achieved after excluding non-adherence and tolerance |

# Is statins the “be-all and end-all” of cholesterol management?

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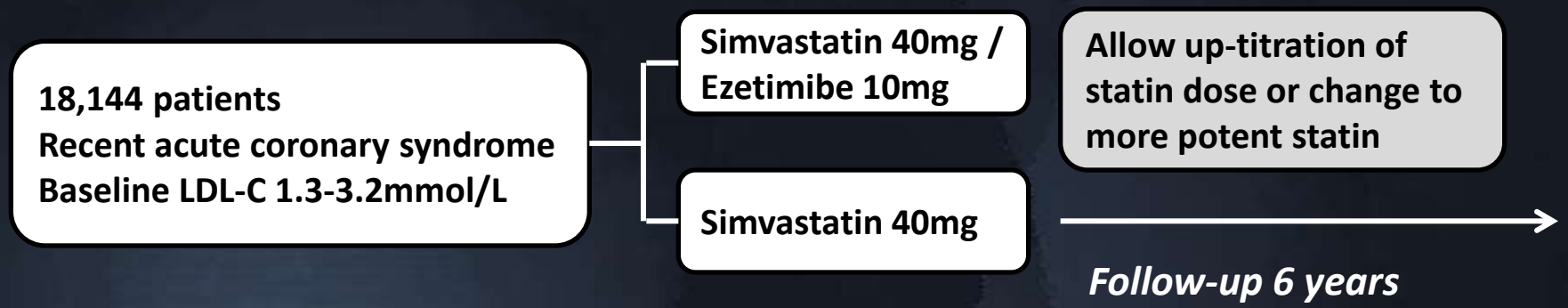
*Adopted from Jarcho JA et al. N Engl J Med 2015*

# IMPROVE-IT: Simvastatin/Ezetimibe combination *vs*. Simvastatin monotherapy in high-risk patients




| | Simvastatin/EZE | Simvastatin |
|---|---|---|
| Age, years | 63.6 | 63.6 |
| Current smoker, % | 32.5 | 33.5 |
| Diabetes, % | 27.1 | 27.3 |
| Baseline statin use, % | 34.6 | 34.3 |
| LDL-C, mmol/L | 2.4 | 2.4 |

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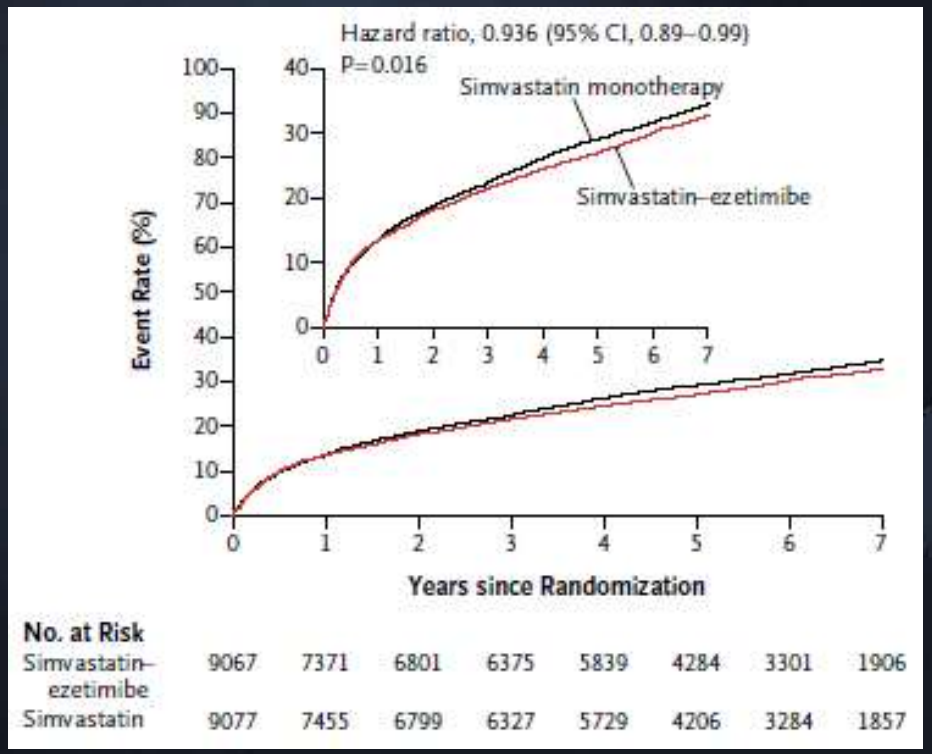
*Cannon CP et al. N Engl J Med 2015*

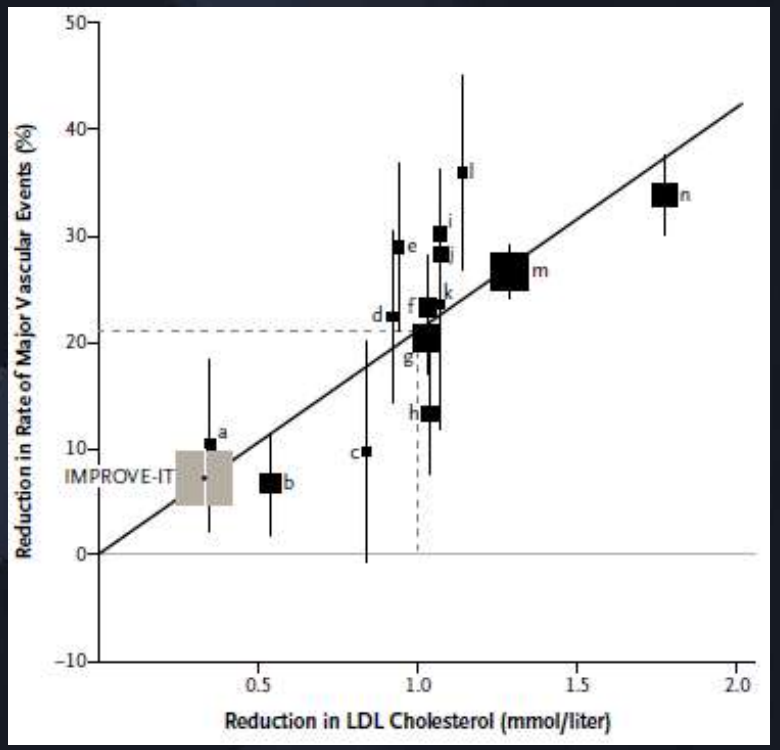
# IMPROVE-IT: Addition of ezetimibe to statin further improves cardiovascular outcome

**Mean LDL-C**

Simvastatin/ezetimibe arm: 1.4 mmol/L

Simvastatin monotherapy arm: 1.8 mmol/L

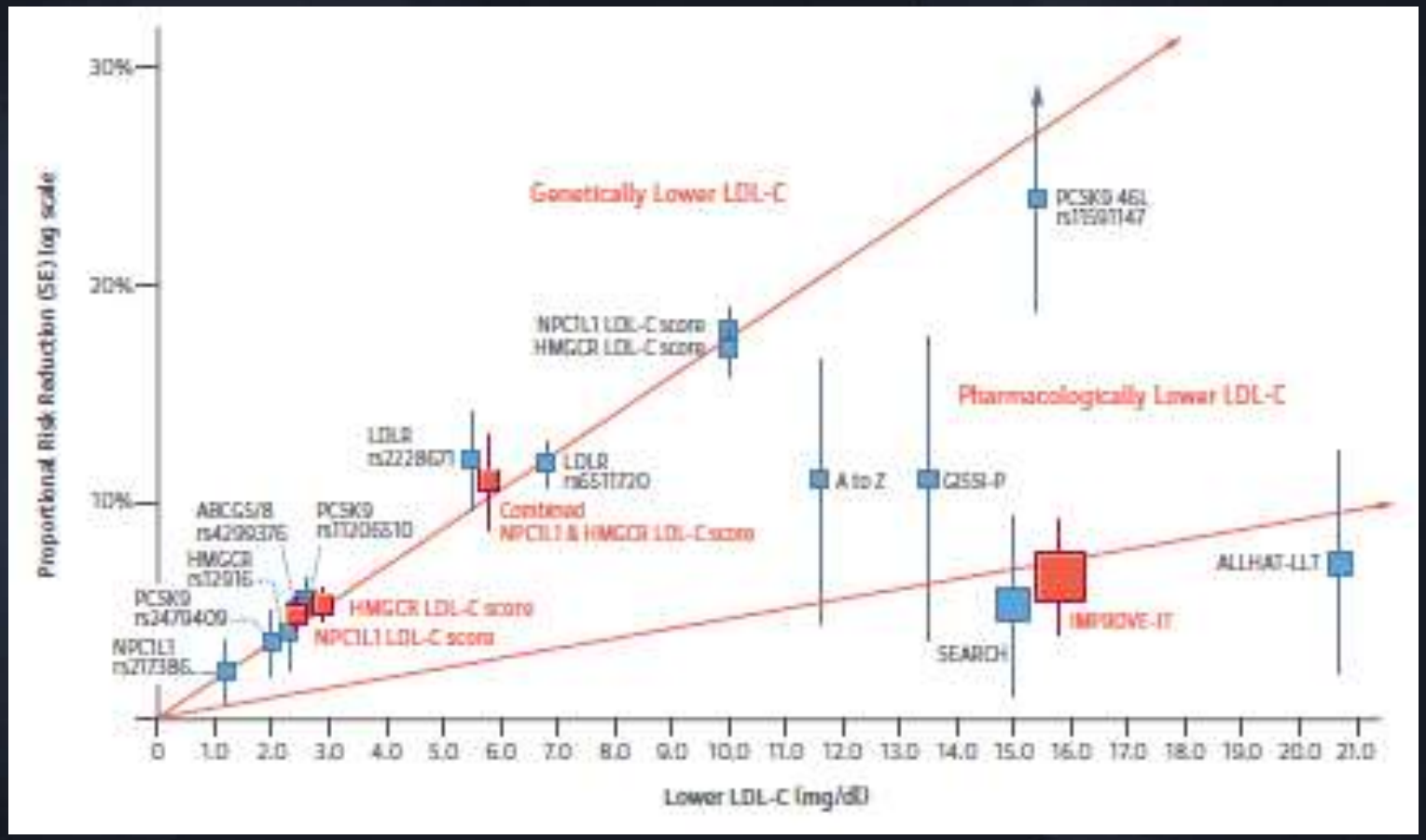





*Cannon CP et al. N Engl J Med 2015*

# Reduction in risk of coronary heart disease is dependent on attained LDL-C

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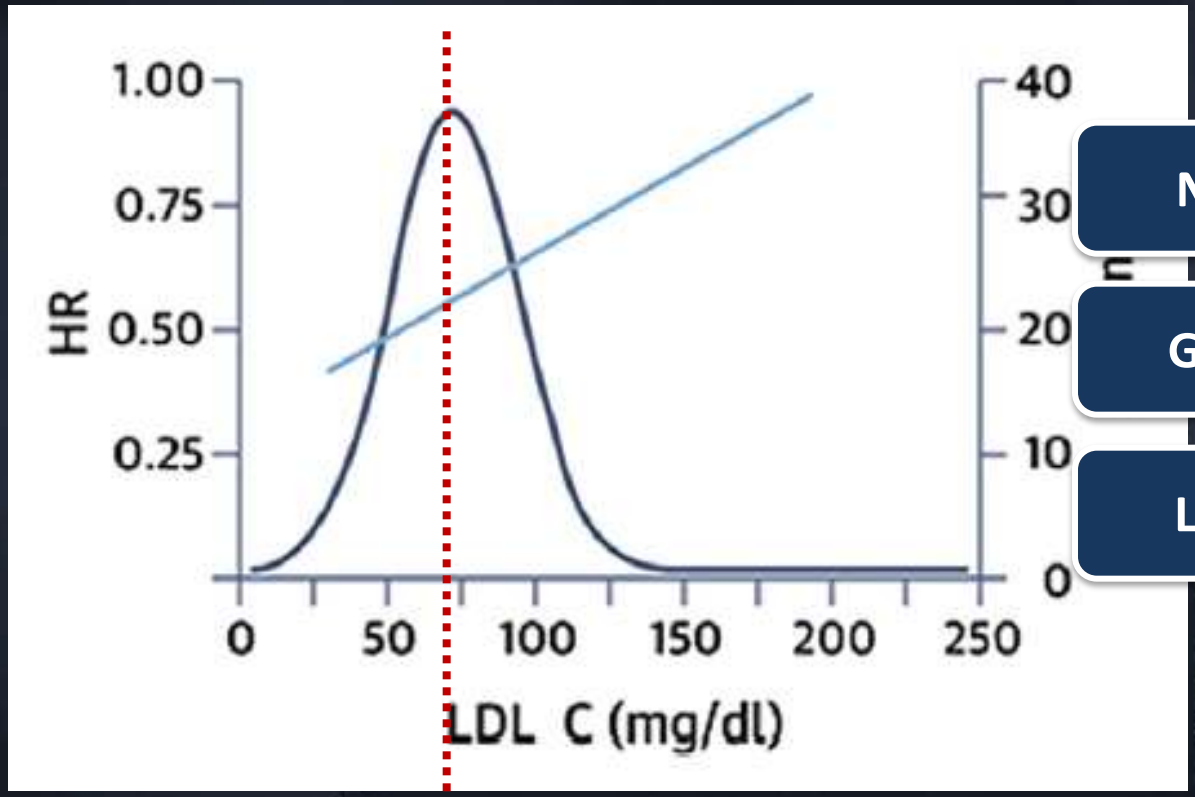
*Ference BA et al. J Am Coll Cardiol 2015*

# Marked inter-individual variation in attainment of LDL-C target with statin

18,677 patients assigned to high intensity statin (atorvastatin 80 mg or rosuvastatin20 mg)




- Non-adherence
- Genetic variants
- Lifestyle factors

40% of patients did NOT reach LDL-C < 1.8mmol/L

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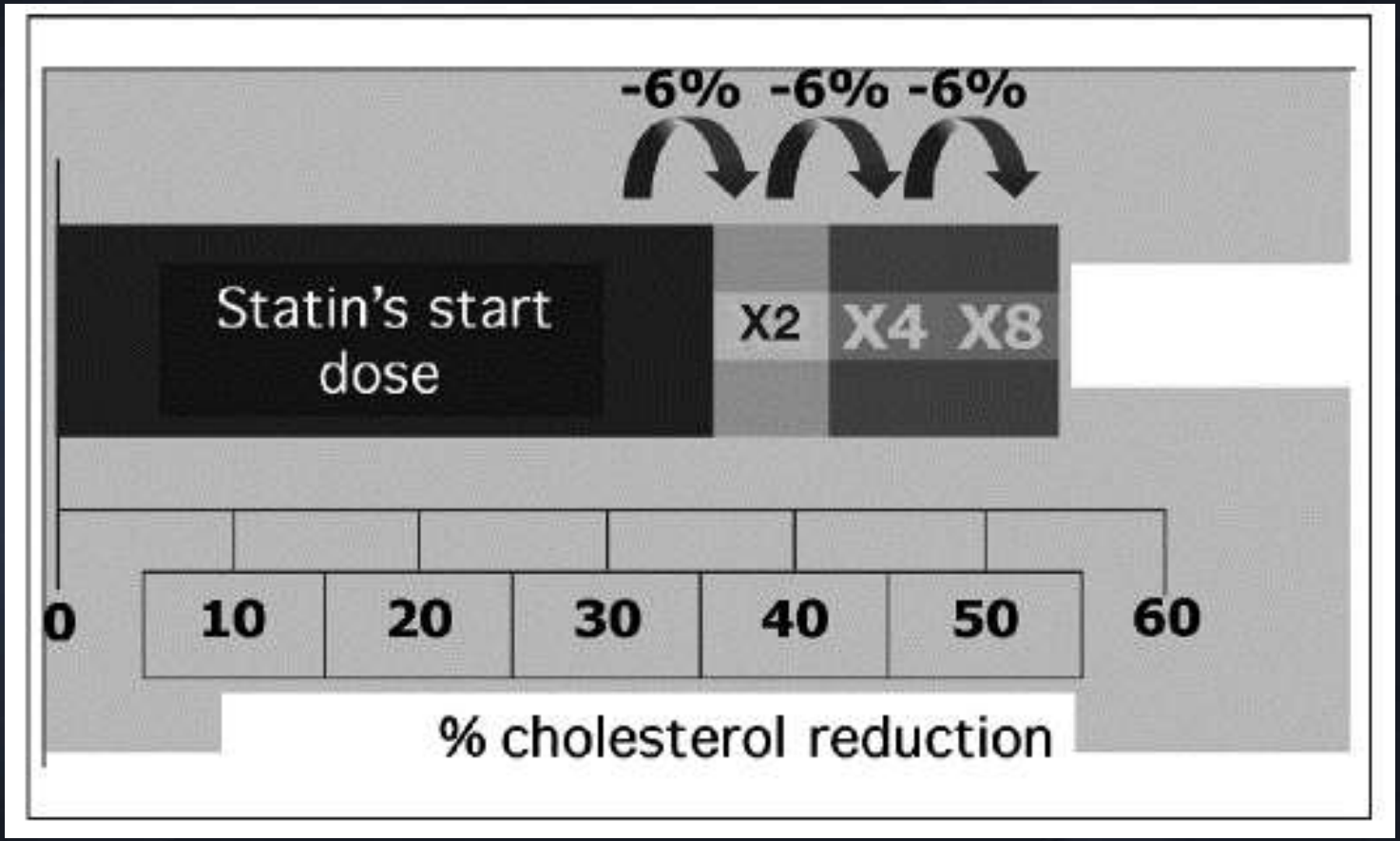
*Boekholdt SM et al. J Am Coll Cardio 2014*

# Rule of 6 in cholesterol reduction

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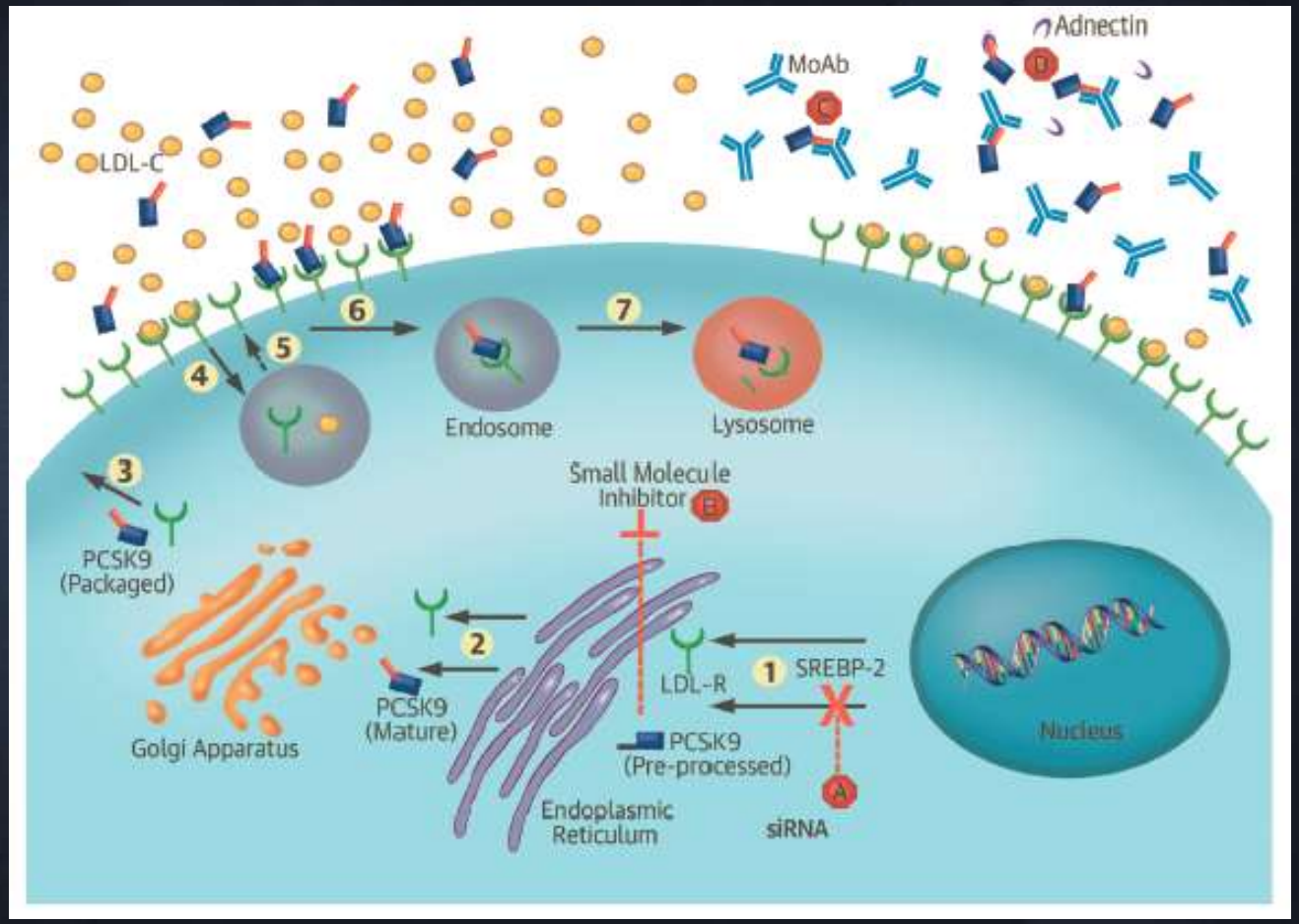
*Adopted from Nodari S et al. Heart Int 2007*
*Leitersdorf E. Eur Heart J Suppl 2001*

# PCSK9-inhibitors interfere with LDL-receptor degradation to increase LDL-receptor availability

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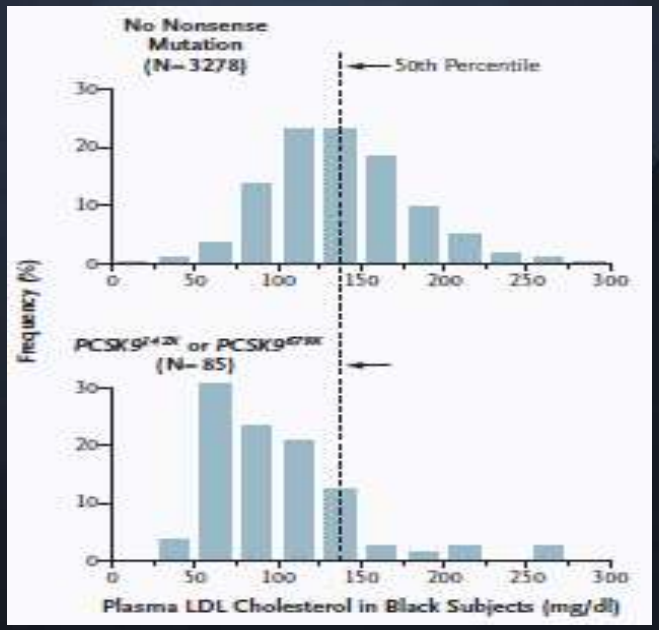
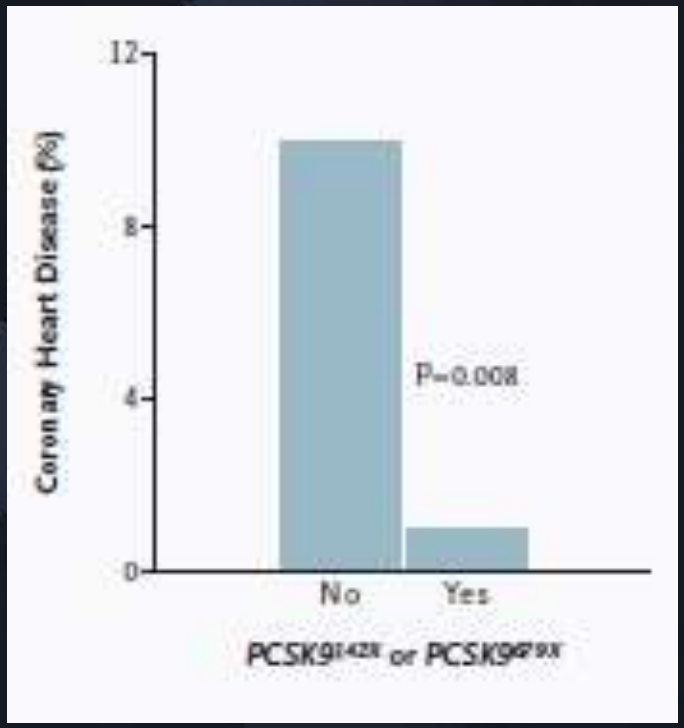
*Adopted from Giugliano RP et al. J Am Coll Cardiol 2015*

# Non-sense mutation in *PCSK9* gene, low LDL-C and protection against coronary heart disease

3,363 black subjects from Atherosclerosis Risk in Communities Study
Genotyped for non-sense mutation (426C→G and 2037C→A) in *PCSK9* gene
Followed-up 15 years for incident coronary heart disease

**2.6% (1 in 40) of black subjects had non-sense mutation.**
**LDL-C was 28% lower in carriers than non-carriers.**




*** HR for CHD was 0.11 (95% CI 0.02-0.81, p=0.03)**

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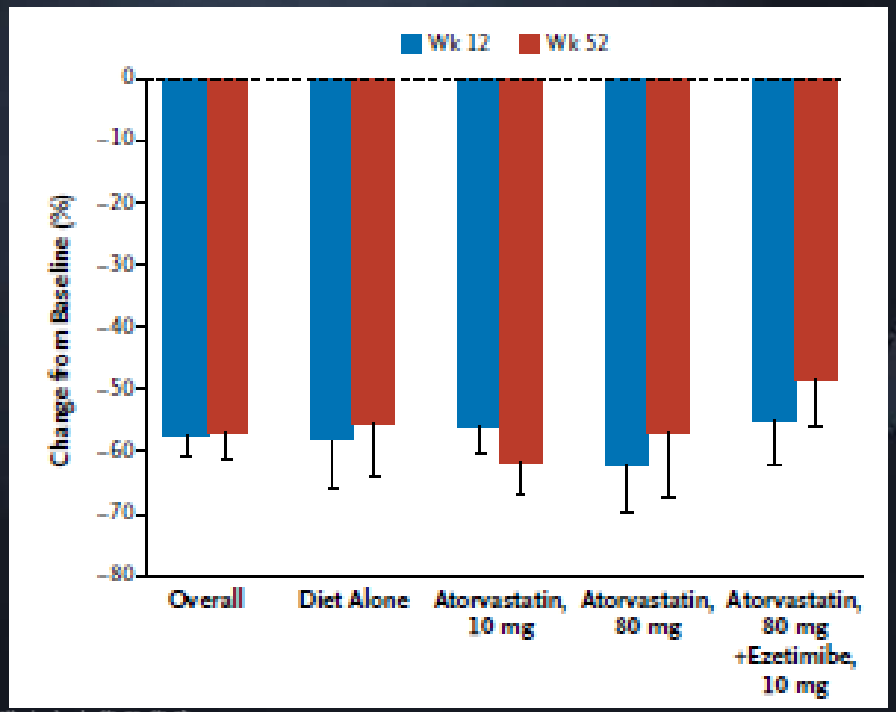
*Cohen JC et al. N Engl J Med 2006*

# PCSK9 inhibition (Evolocumab) substantially lowers LDL-C beyond statins

901 patients with hypercholesterolaemia
Background lipid lowering drug: Atorvastatin 10-80 mg ± Ezetimibe 10 mg
Intervention: Evolocumab 420 mg SC 4-weekly or placebo for 52 weeks

**Percent reduction from baseline in LDL-C in Evolocumab vs. placebo by baseline lipid lowering therapy**




**Baseline LDL-C**
Whole cohort: 2.69 mmol/L

**Study close LDL-C**
Evolocumab: 1.32 mmol/L
Placebo: 2.77 mmol/L

**Proportion with LDL-C <1.8 mmol/L**
Evolocumab: 82.3%
Placebo: 6.4%

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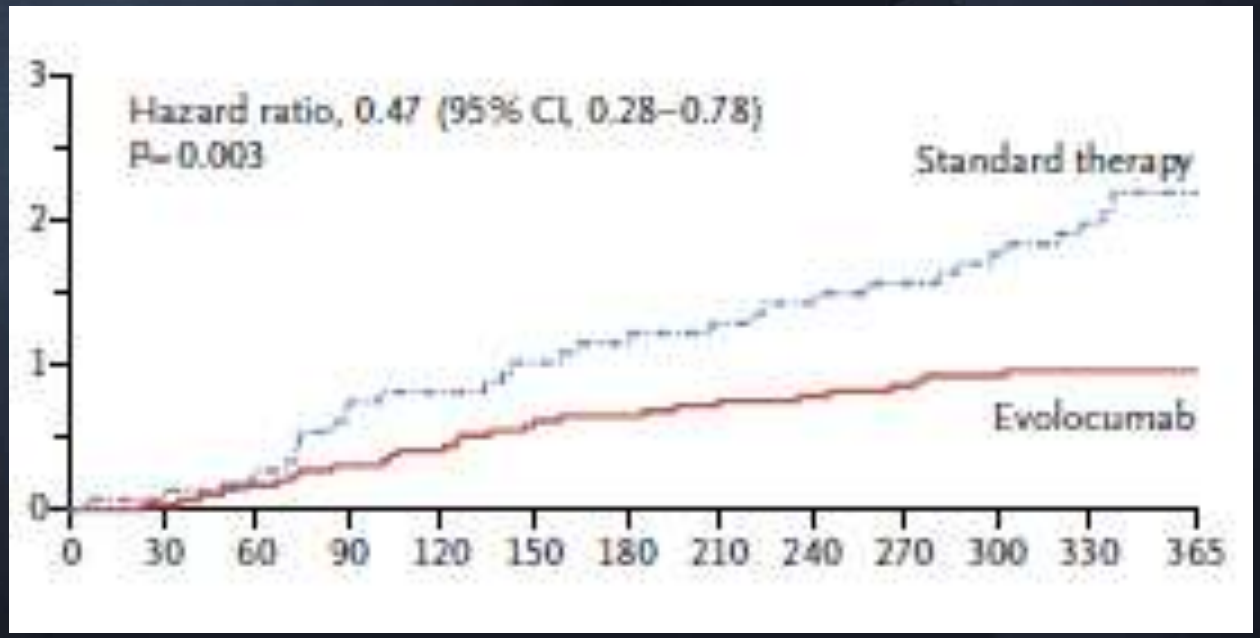
*Blom DJ et al. for DESCARTES Investigators. N Engl J Med 2014*

# PCSK9 inhibition (Evolocumab) may reduce cardiovascular events

Open-label extension study of 4,465 patients previously participated in phase 2 or 3 studies
Intervention: Evolocumab SC 140mg 2-weekly or 420mg monthly vs. standard therapy
Evolocumab reduced LDL-C by 61% compared to standard therapy

**Cumulative incidence of cardiovascular events over 12 months**

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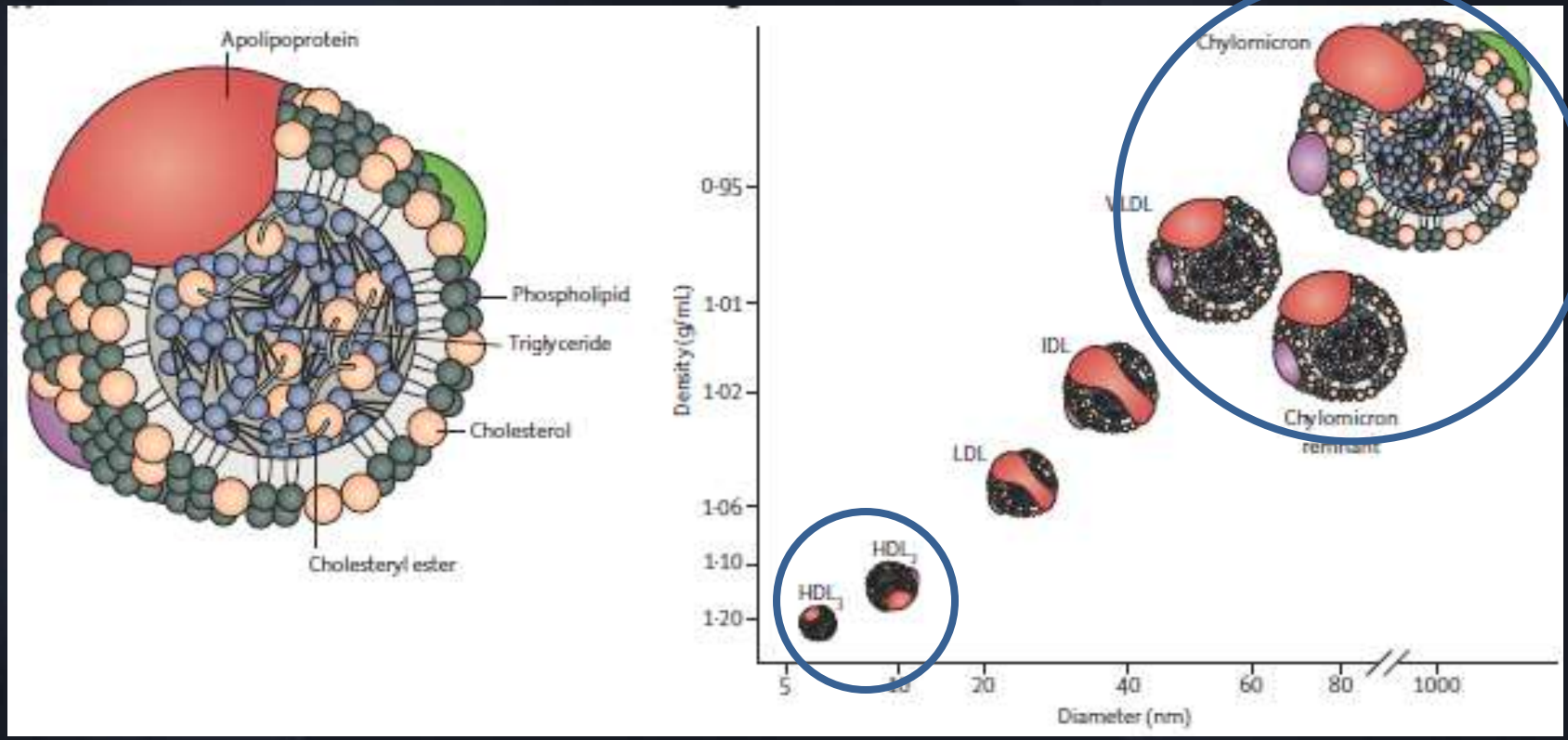
*Sabatine MS et al, for OSLER Investigators. N Engl J Med 2015*

# What about non-LDL cholesterol?

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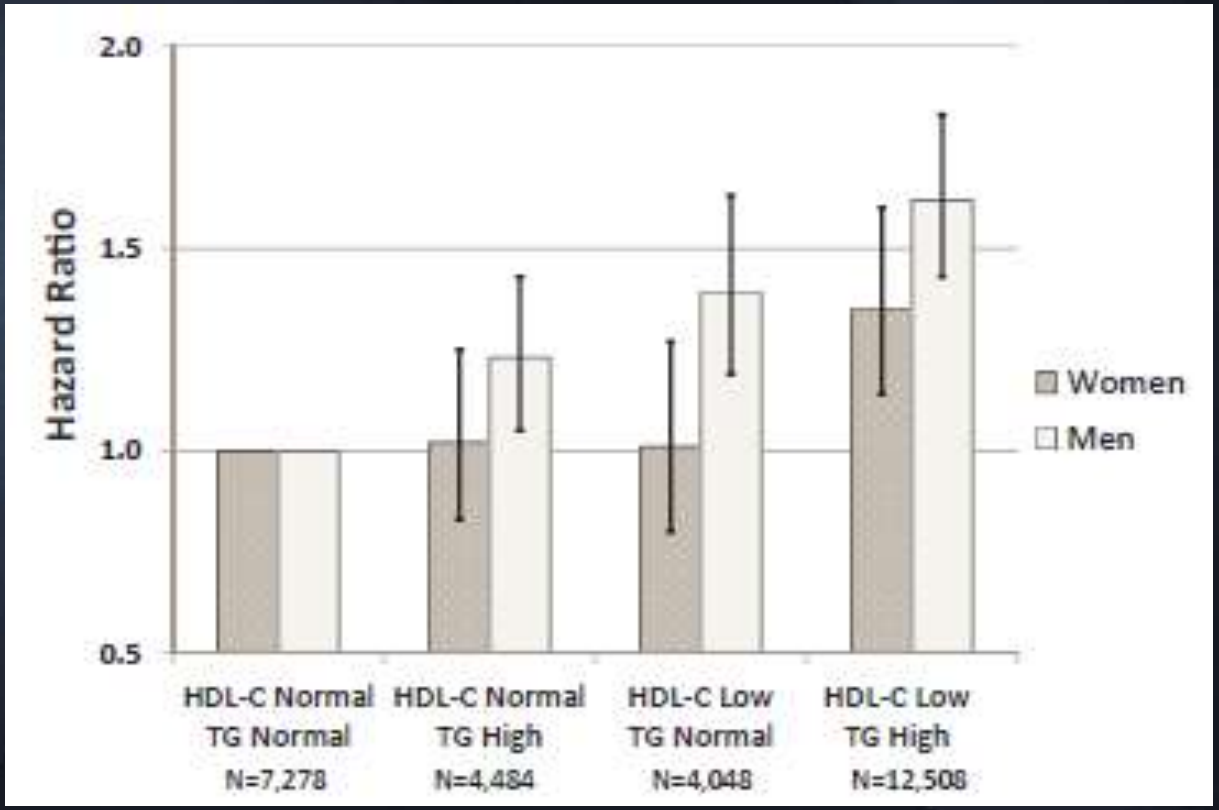
*Adopted from Ridker PM. Lancet 2014*

# Metabolic dyslipidaemia and risk of coronary heart disease

**28,318 adults (30-90 years) with diabetes of Kaiser Permanente Northern California LDL<2.6 mmol/L and no history of CHD.**

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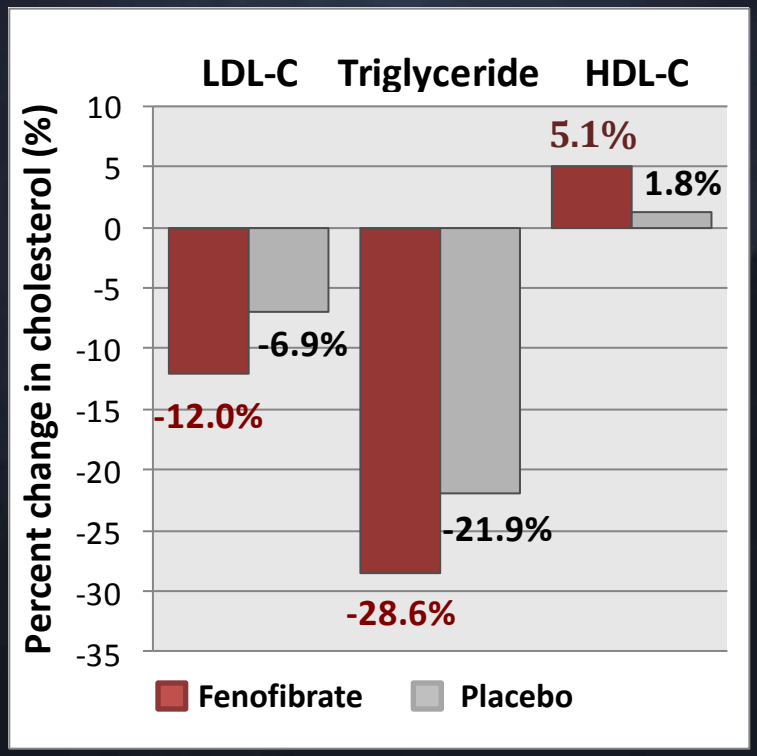
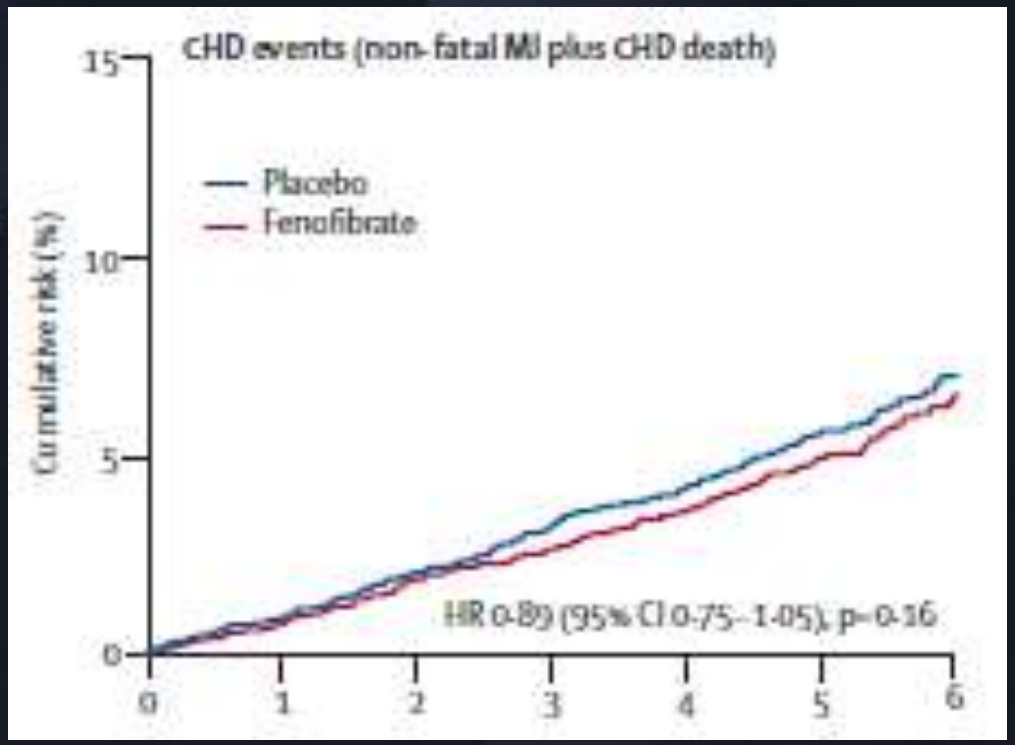
*Rana JS et al. Am J Cardiol 2015*

# FIELD: Fenofibrate did not reduce composite outcome of fatal & non-fatal coronary heart disease

9795 patients with T2D, not on statins at baseline
Intervention: Fenofibrate 200mg daily or placebo
Primary endpoint: non-fatal and fatal CHD, followed-up 5 years

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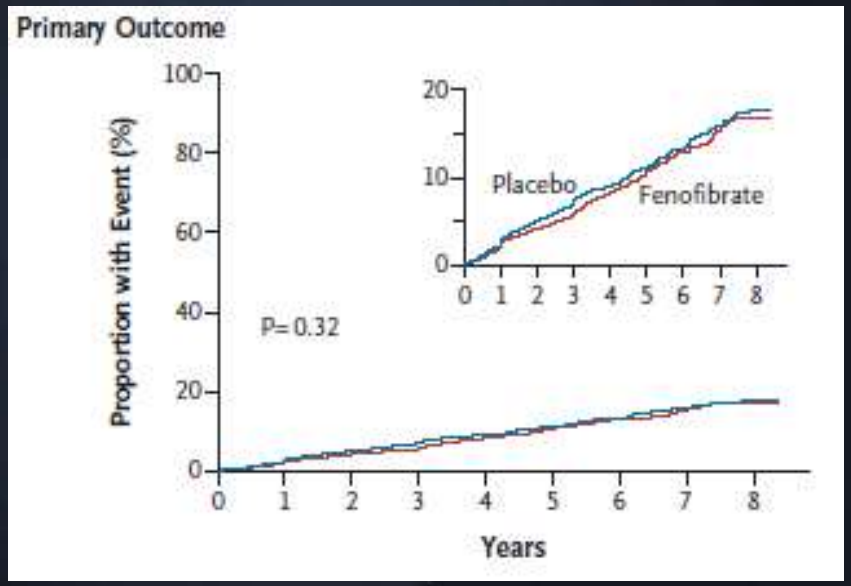
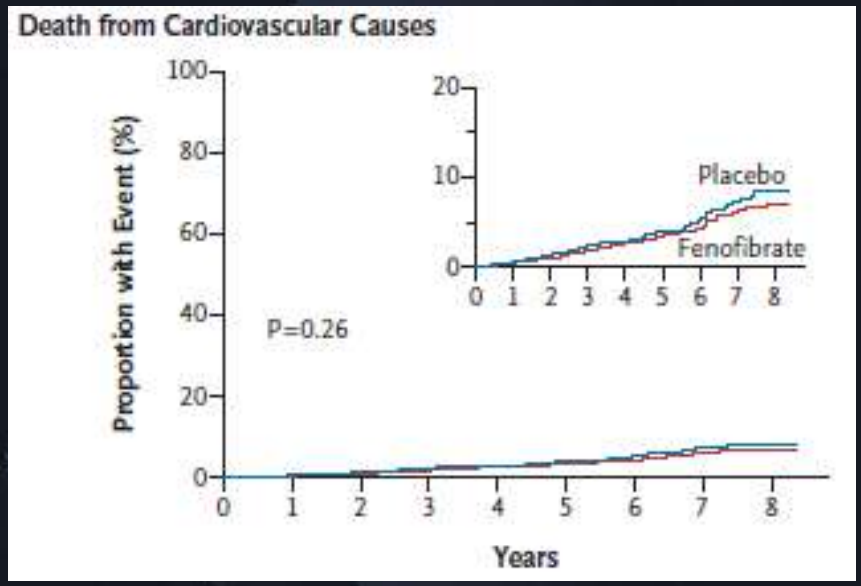
*The FIELD Study Investigators. Lancet 2005*

# ACCORD: Fenofibrate did not reduce fatal or non-fatal cardiovascular disease in T2D

5518 patients with T2D on simvastatin as background therapy
Intervention: Fenofibrate 200mg daily or placebo for 4.7 years
Primary outcome: non-fatal MI, non-fatal stroke, death from CVD




*No difference in LDL-C between fenofibrate and placebo
**Fenofibrate lowered triglyceride and raised HDL-C more than placebo

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*Ginsberg HN et al for ACCORD Study Group. N Engl J Med 2010*

# Extended-release niacin: To be or not to be?

| | AIM-HIGH | HPS2-THRIVE |
|---|---|---|
| Patients | 3,414 patients with CVD | 25,673 patients with CVD |
| Baseline LDL-C | 1.92 mmol/L | 1.64 mmol/L |
| Intervention | Niacin or placebo | Niacin-laropiprant or placebo |
| Background lipid-lowering drugs | Simvastatin variable dose ± Ezetimibe 10mg | Simvastatin 40mg ± Ezetimibe 10mg |
| **Changes in lipid levels** | | |
| LDL-C | -13.6% vs -7.6% | - 0.25 mmol/L |
| HDL-C | 25.0% vs 11.8% | + 0.16 mmol/L |
| Triglyceride | -30.8% vs -9.9% | - 0.37 mmol/L |

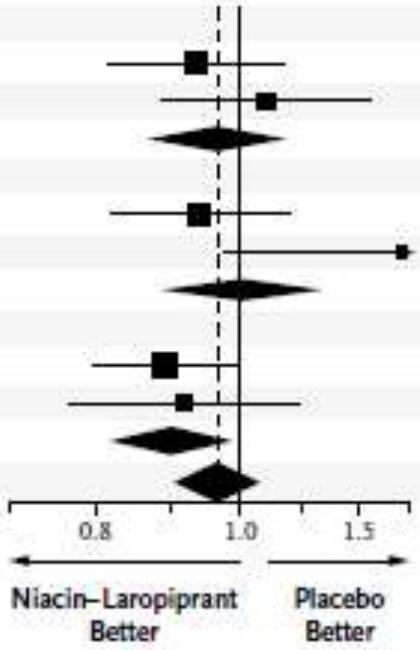


*Boden WE et al for AIM-HIGH Investigators. N Engl J Med 2012*
*Landray MJ et al for HPS2-THRIVE Collaborative Group. N Eng. J Med 2014*

# Niacin failed to reduce fatal and non-fatal cardiovascular events

**Primary outcome: non-fatal MI, death from coronary causes, any stroke, arterial revascularization**

| Type of Major Vascular Event | Niacin–Laropiprant (N=12,838) | Placebo (N=12,835) | Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of participants with event (%)* | | | |
| Major coronary event | | | | |
| Nonfatal myocardial infarction | 402 (3.1) | 431 (3.4) | | |
| Death from coronary cause | 302 (2.4) | 291 (2.3) | | |
| Any major coronary event | 668 (5.2) | 694 (5.4) | 0.96 (0.87–1.07) | 0.51 |
| Stroke | | | | |
| Nonhemorrhagic stroke | 389 (3.0) | 415 (3.2) | | |
| Hemorrhagic stroke | 114 (0.9) | 89 (0.7) | | |
| Any stroke | 498 (3.9) | 499 (3.9) | 1.00 (0.88–1.13) | 0.56 |
| Revascularization procedure | | | | |
| Coronary revascularization | 591 (4.6) | 664 (5.2) | | |
| Noncoronary revascularization | 236 (1.8) | 258 (2.0) | | |
| Any revascularization procedure | 807 (6.3) | 897 (7.0) | 0.90 (0.82–0.99) | 0.03 |
| Any major vascular event | 1696 (13.2) | 1758 (13.7) | 0.96 (0.90–1.03) | 0.29 |

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*Landray MJ et al for HPS2-THRIVE Collaborative Group. N Eng. J Med 2014*

# Treatment of hypertriglyceridaemia: What do guidelines say?

| GUIDELINE | Recommendation |
|---|---|
| **ACC/AHA 2013** | No evidence-based recommendations for treatment of hypertriglyceridaemia to reduce CVD risk.<br>Endorse treatment of patients with fasting triglyceride >5.6mmol/L to prevent pancreatitis. |
| **ADA 2016** | Combination therapy (statin/fibrate) has not been shown to provide additional CV benefit above statin alone and not recommended. |
| **NICE 2014** | Do not routinely offer fibrates for prevention of CVD for primary prevention, secondary prevention, in people with chronic kidney disease and in people with type 1 or type 2 diabetes. |
| **ESC 2012** | Recommend treatment to lower triglyceride in patient at high CV risk and triglyceride >2.3mmol/L. |

ACC, American College of Cardiology; AHA, American Heart Association; ADA, American Diabetes Association; NICE, National Clinical Guideline Centre; ESC, European Society of Cardiology

# Treatment of low HDL-cholesterol: What do guidelines say?

| GUIDELINE | Recommendation |
|---|---|
| **ACC/AHA 2013** | HDL-C is not a target for therapy. |
| **ADA 2016** | Combination therapy (statin/fibrate) has not been shown to provide additional CV benefit above statin alone and not recommended. |
| **NICE 2014** | Do not offer nicotinic acid for prevention of CVD for primary prevention, secondary prevention, in people with chronic kidney disease and in people with type 1 or type 2 diabetes. |
| **ESC 2012** | Nicotinic acid is currently the most efficient drug to raise HDL-C and should be considered. (Class II1 evidence) |

ACC, American College of Cardiology; AHA, American Heart Association; ADA, American Diabetes Association; NICE, National Clinical Guideline Centre; ESC, European Society of Cardiology

# Summary

- Statin remains the first line treatment in lipid lowering in primary and secondary prevention.
- Recent evidences suggest that statin and non-statin LDL lowering drugs provide similar cardiovascular benefits.
- PCSK9 inhibitors substantially reduce LDL cholesterol and may become an important addition to therapeutic armamentarium on CV risk management especially for high risk subjects.
- Available evidences do not support the routine use of fibrates and nicotinic acid for CV risk reduction.

# THANK YOU

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