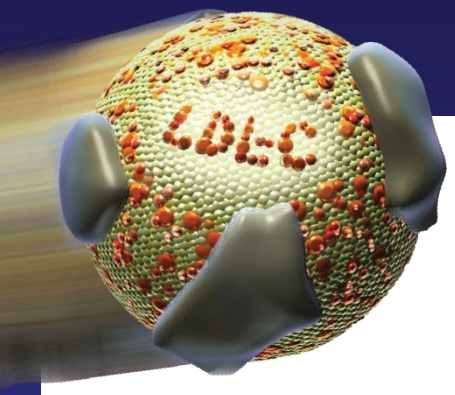


Hyperlipidemia Treatment in Patients with Diabetes

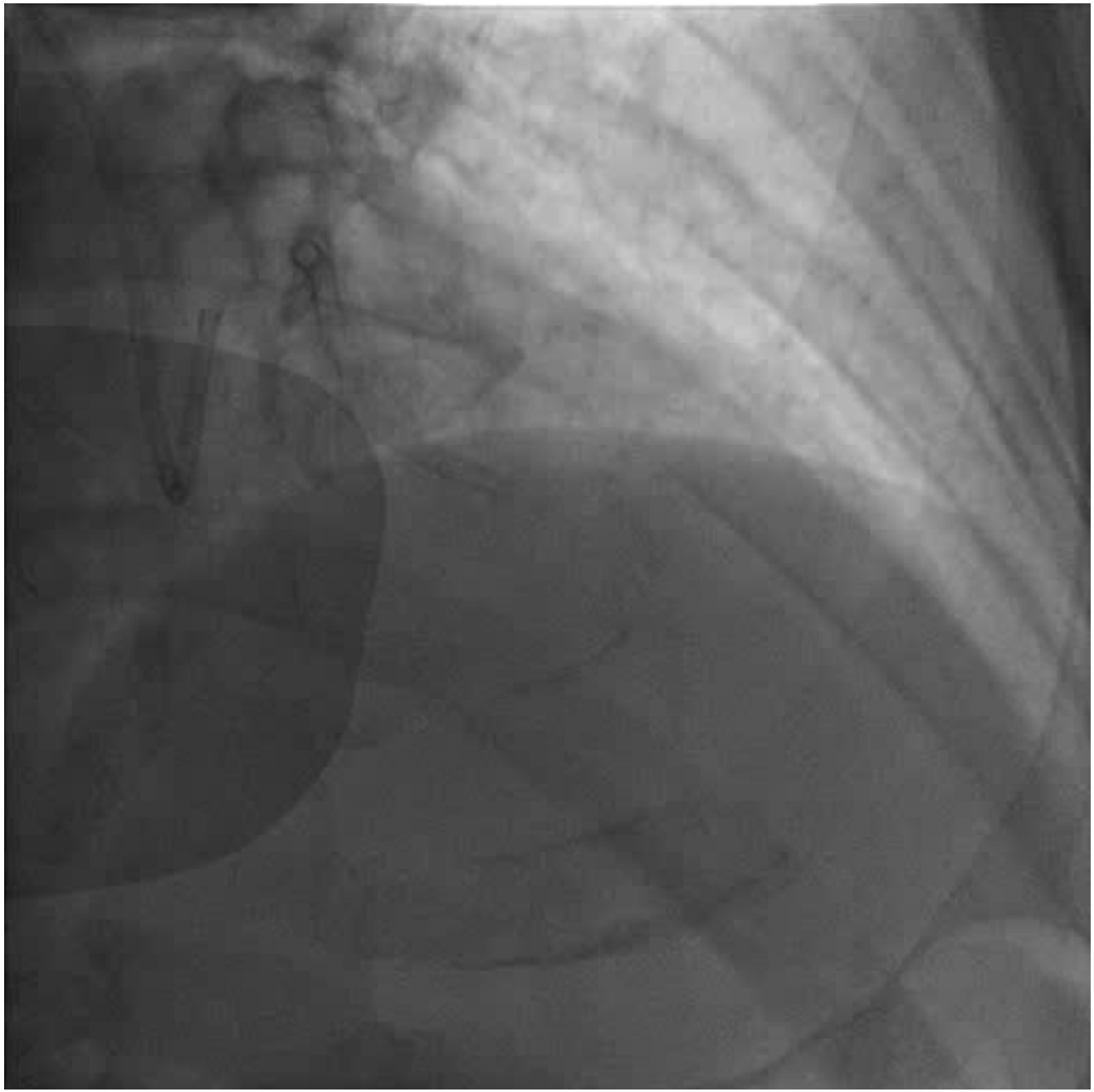
Speaker: 黃偉杰醫師

新北市聯醫心臟科主治醫師
臺北榮總心臟科主治醫師
陽明大學醫學系部定講師

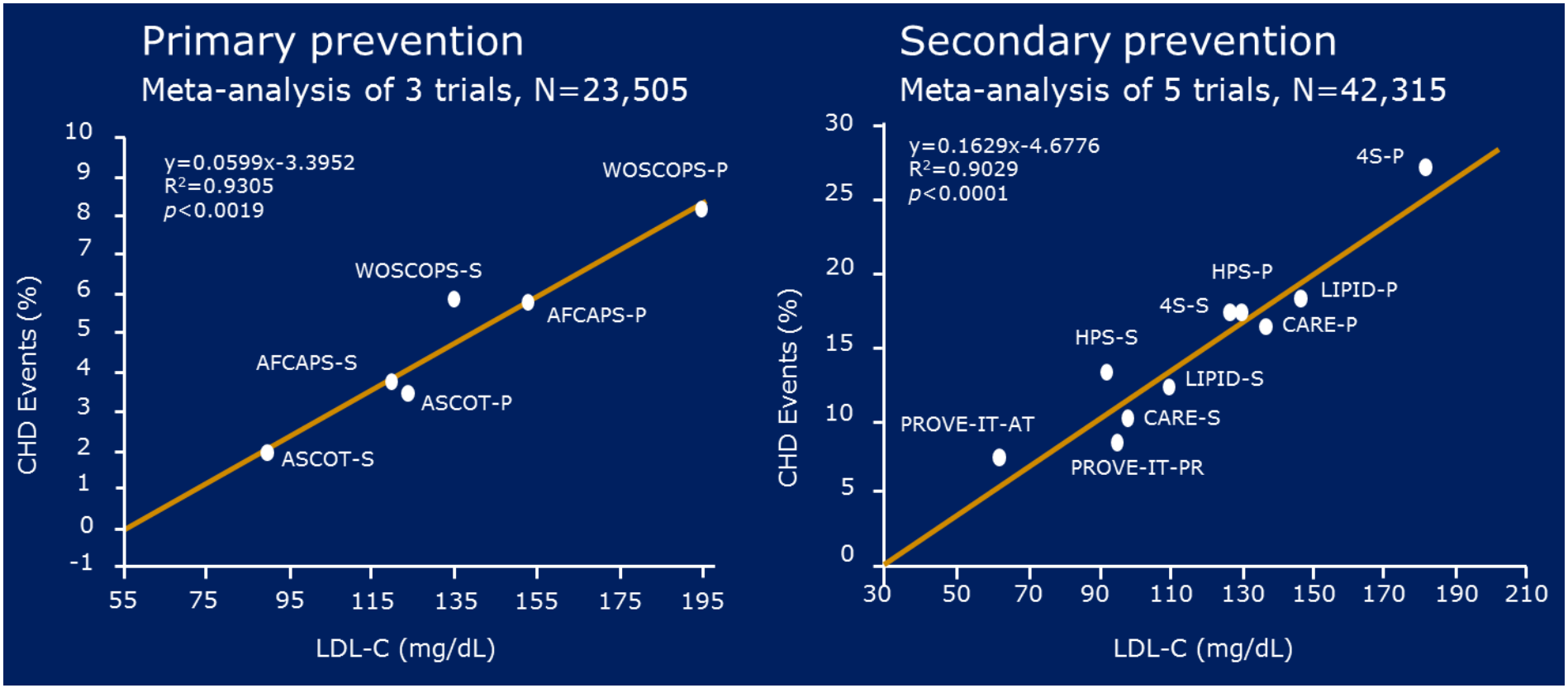
全民健康保險降膽固醇藥物給付規定表

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
1. 有急性冠狀動脈症候群病史 2. 曾接受心導管介入治療或外科冠動脈搭橋手術之冠狀動脈粥狀硬化患者(108/2/1)	與藥物治療可並行	LDL-C≧70mg/dL	LDL-C<70mg/dL	第一年應每3-6個月抽血檢查一次，第二年以後應至少每6-12個月抽血檢查一次，同時請注意副作用之產生如肝功能異常，橫紋肌溶解症。
心血管疾病或糖尿病患者	與藥物治療可並行	TC≧160mg/dL 或 LDL-C≧100mg/dL	**TC＜160mg/dL 或 LDL-C＜100mg/dL**	
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL 或 LDL-C≧130mg/dL	TC＜200mg/dL 或 LDL-C＜130mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL 或 LDL-C≧160mg/dL	TC＜240mg/dL 或 LDL-C＜160mg/dL	
0個危險因子	給藥前應有3-6個月非藥物治療	LDL-C≧190mg/dL	LDL-C＜190mg/dL	

全民健康保險藥物給付項目及支付標準之藥品給付規定-108年版



RCT data support a *direct linear relationship* between *LDL-C levels and CHD event* rates

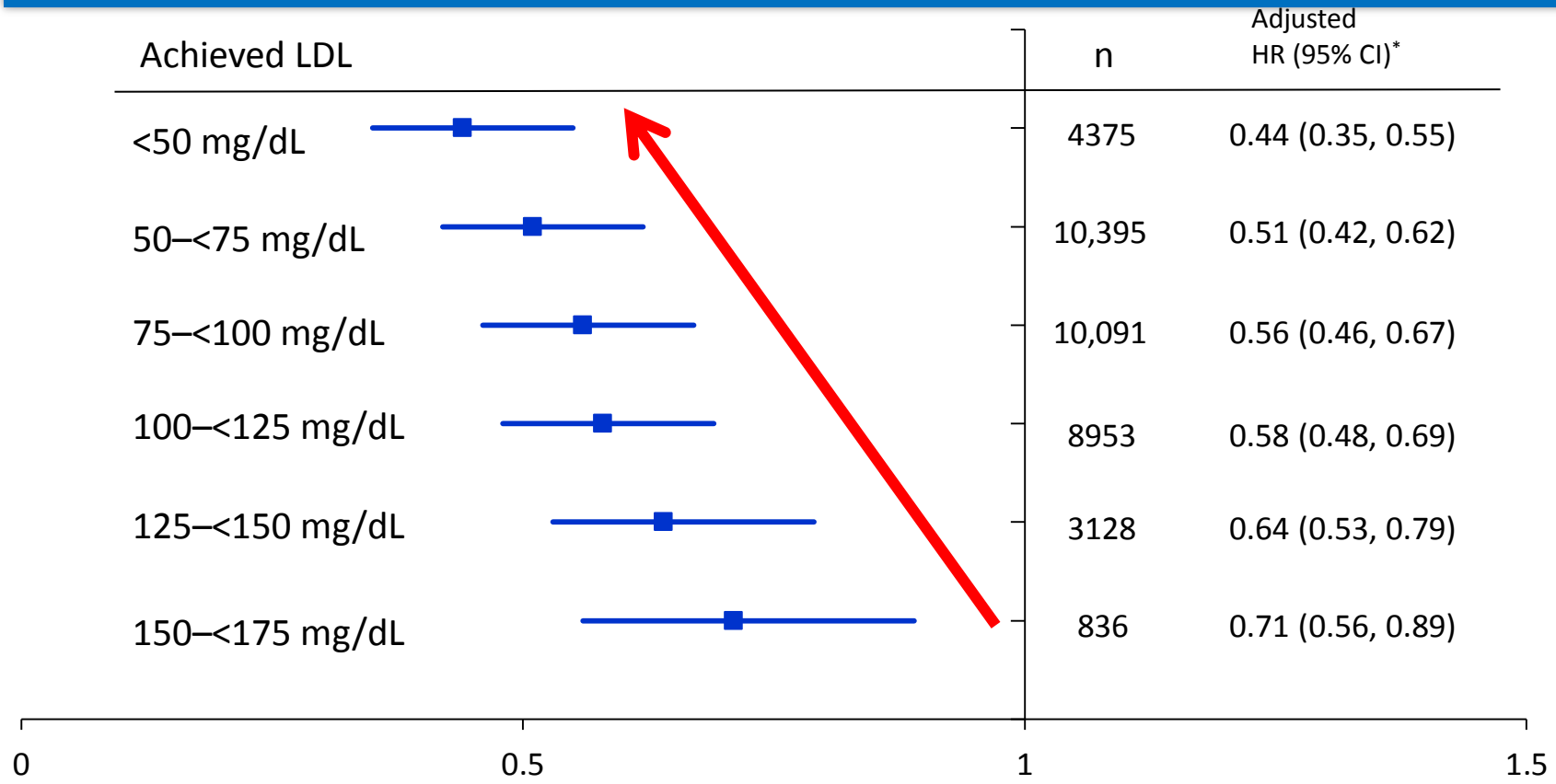


There is no clear lower 'limit' for LDL-C reduction and the related benefits to CHD reduction

Figure adapted from 1. O'Keefe JH, et al. J Am Coll Cardiol. 2004;43(11):2142–2146. 4S, Scandinavian Simvastatin Survival Study; AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; AT, atorvastatin arm; CARE, Cholesterol and Recurrent Events Trial; HPS, Heart Protection Study; LIPID, Long-term intervention with Pravastatin in ischaemic Disease Trial; P, placebo arm; PR, pravastatin arm; PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Trial; S, statin arm; WOSCOPS, West of Scotland Cardiac Outcomes Study

Risk for Major CV Events, by Achieved LDL-C Concentration

Patients achieving LDL-C <50 mg/dL have a lower risk for major cardiovascular events than those achieving moderately low levels (50–75 mg/dL or 75–100 mg/dL)



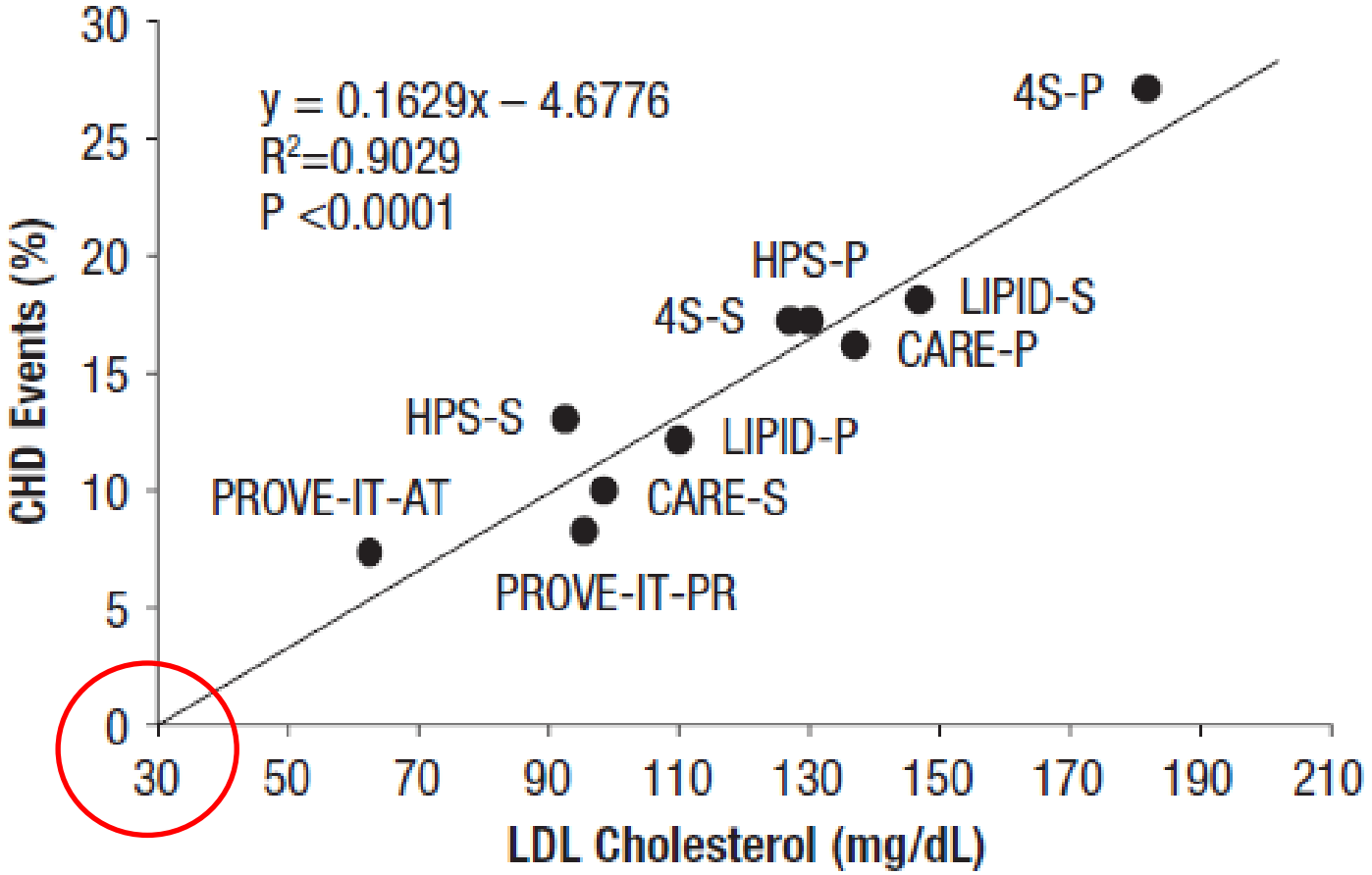
*Adjusted for sex, age, smoking status, presence of diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol concentration, and trial. The highest LDL-C category (≥175 mg/dL; ≥4.52 mmol/L) was used as the reference category.

Boekholdt SM, et al. *J Am Coll Cardiol* 2014:64(5)485–494.

Coronary Heart Disease Event Rates in *ACS & Secondary Prevention* Trials

5 years in duration (except the PROVE-IT study for 2 years) were directly proportional to LDL-C levels.

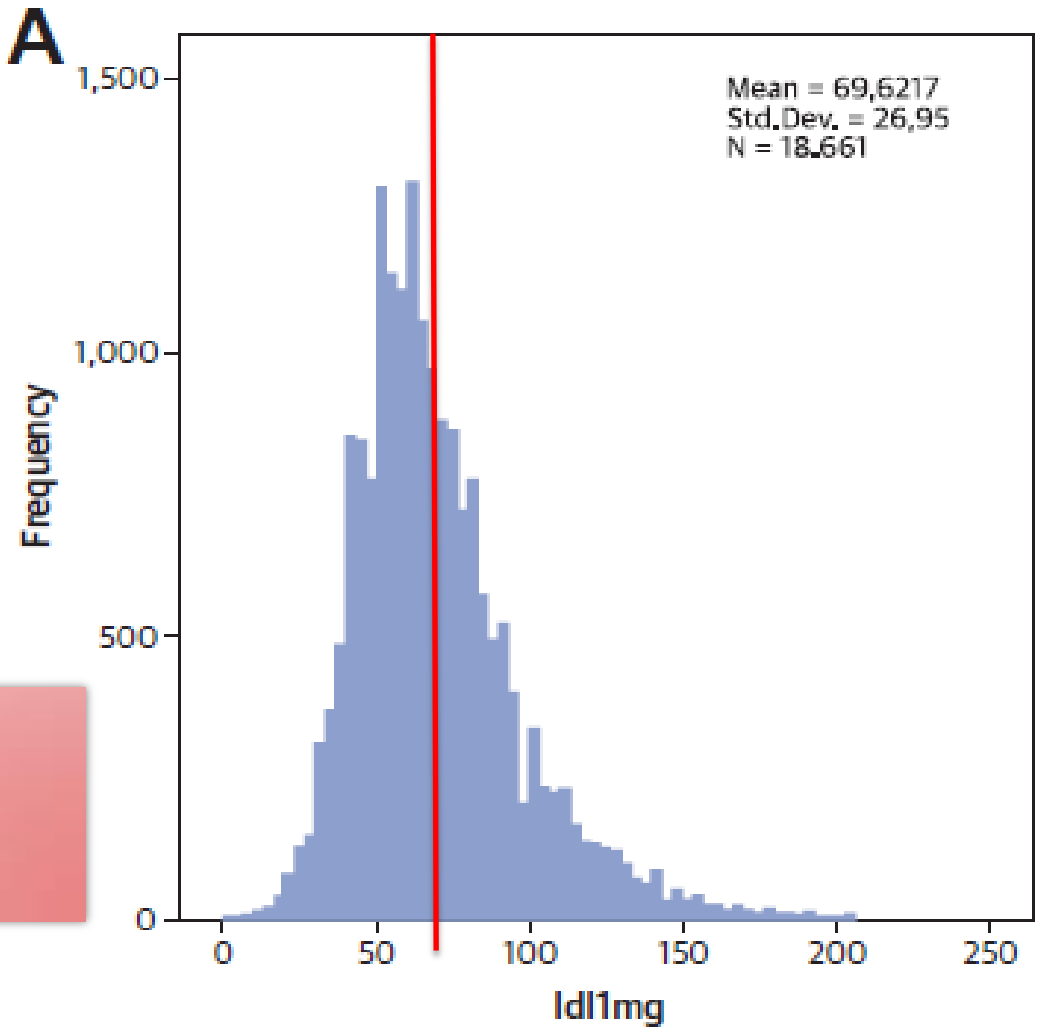
The event rate is predicted to approach 0 at LDL of 30 mg/dL



Updated from O'Keefe J et al. *J Am Coll Cardiol*. 2004;43:2142-46; Lepor NE, KereiakesAm DJ Health Drug Benefits.2015;8(9):483-488.

Distribution of achieved LDL-C levels on *high-dose statin therapy*

A meta-analysis including individual patient data (N=38,153) from 8 randomised controlled statin trials;
18,677 patients assigned to high-dose statin; atorvastatin 80mg (TNT, IDEAL or SPARCL) or rosuvastatin 20mg (JUPITER)



12.7% not reach LDL-C <100 mg/dl
40.4% not reach LDL-C <70 mg/dl
78.3% not reach LDL-C <50 mg/dl

Boekholdt SM, et al. J Am Coll Cardiol 2014; 64:485–94.

Diabetic Dyslipidemia

Individuals with DM are at increased risk for CVD

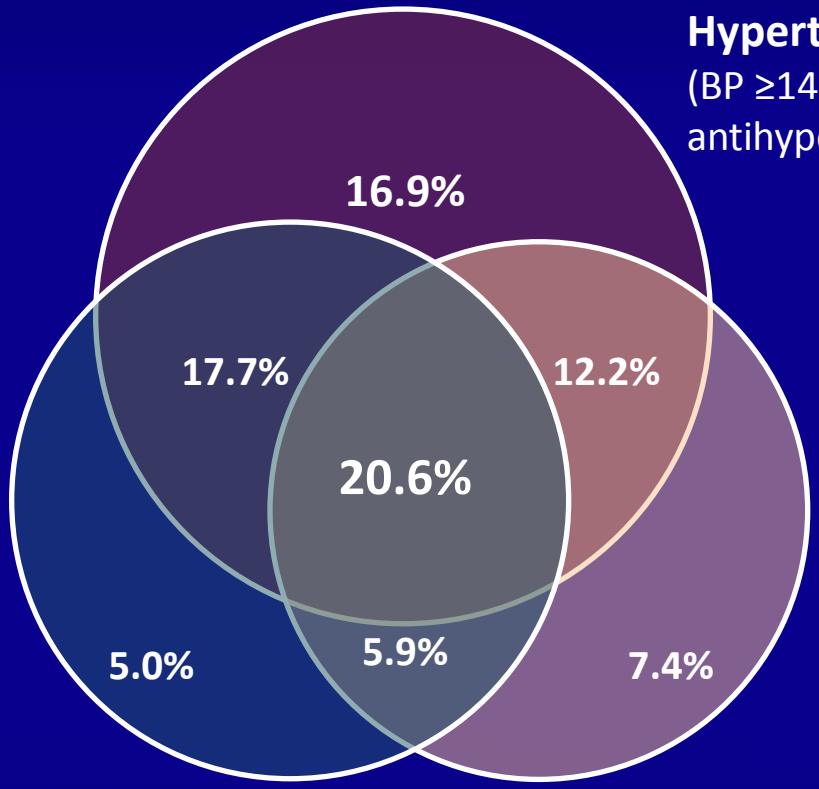
- **People with diabetes**
  - ➔ **2X – 4X** more likely to develop CVD than people without DM. **CVD is leading cause of mortality for people with DM**
  - ➔ Have ↗ risk of CVD (HTN, abnormal blood lipids and obesity more frequent)
  - ➔ Are **2X-6X** more likely to have TIA compared to people without DM
  - ➔ Have **2X – 3X** greater risk of HF compared to people without DM
  - ➔ have A **HIGHER RISK for ATHEROSCLEROSIS** development at younger age and progression, **WORSE** prognosis, and **HIGHER RATE of recurrent CVD**

- The risk of death due to CHD is **1.9-times greater for every 10 years a patient has diabetes**

Go AS et al. Circulation. 2014;129(3):e28-e292.Source: World Heart Federation. Cardiovascular Diseases Risk Factors http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors/diabetes/. Accessed October 14, 2016.

Comorbid conditions in people with T2DM

US-NHANES 1999-2004
(N=984)



Hypertension
(BP ≥140/90 mm Hg or taking antihypertensive medication)

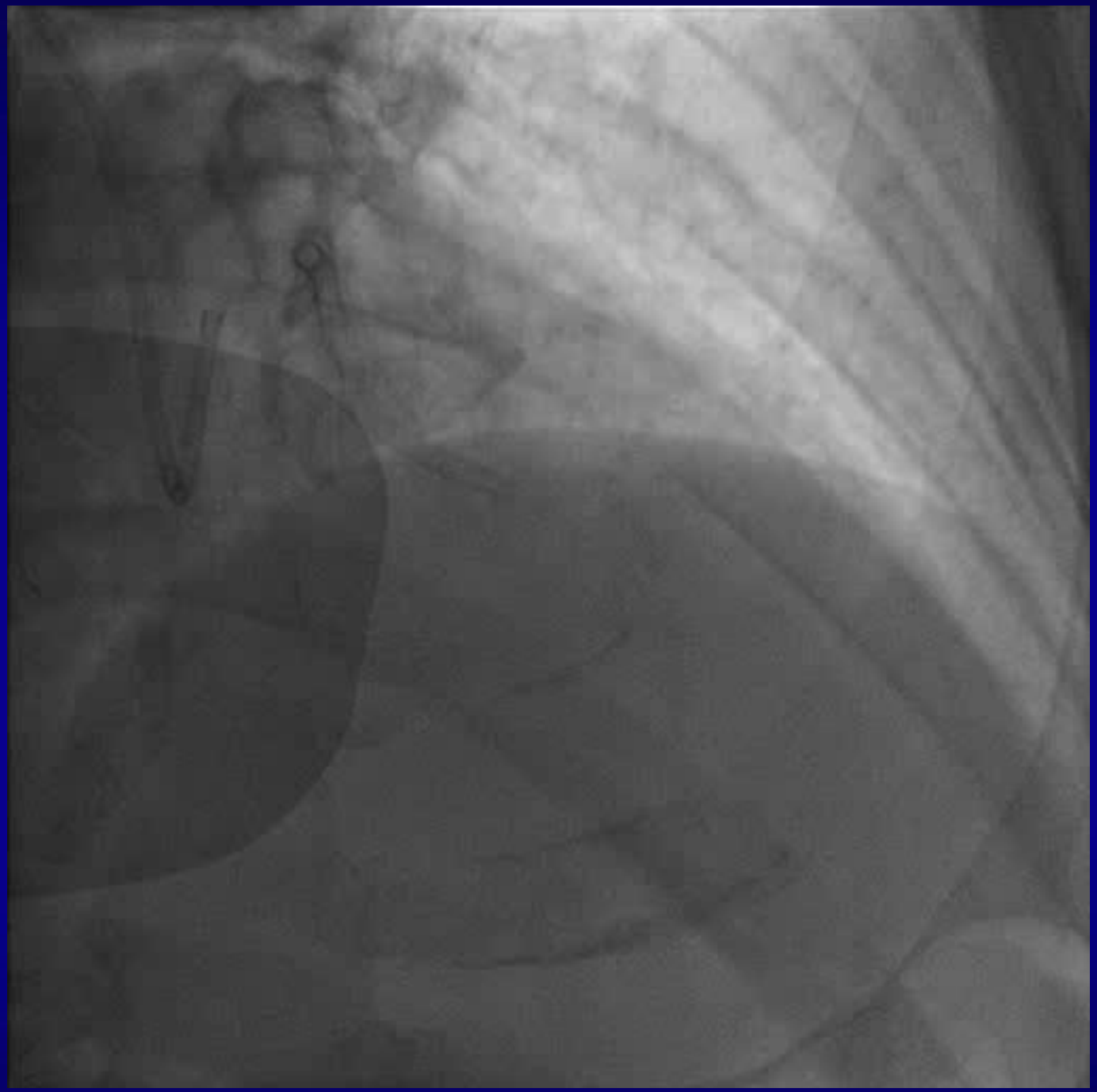
Obesity
(BMI ≥30 kg/m^2)

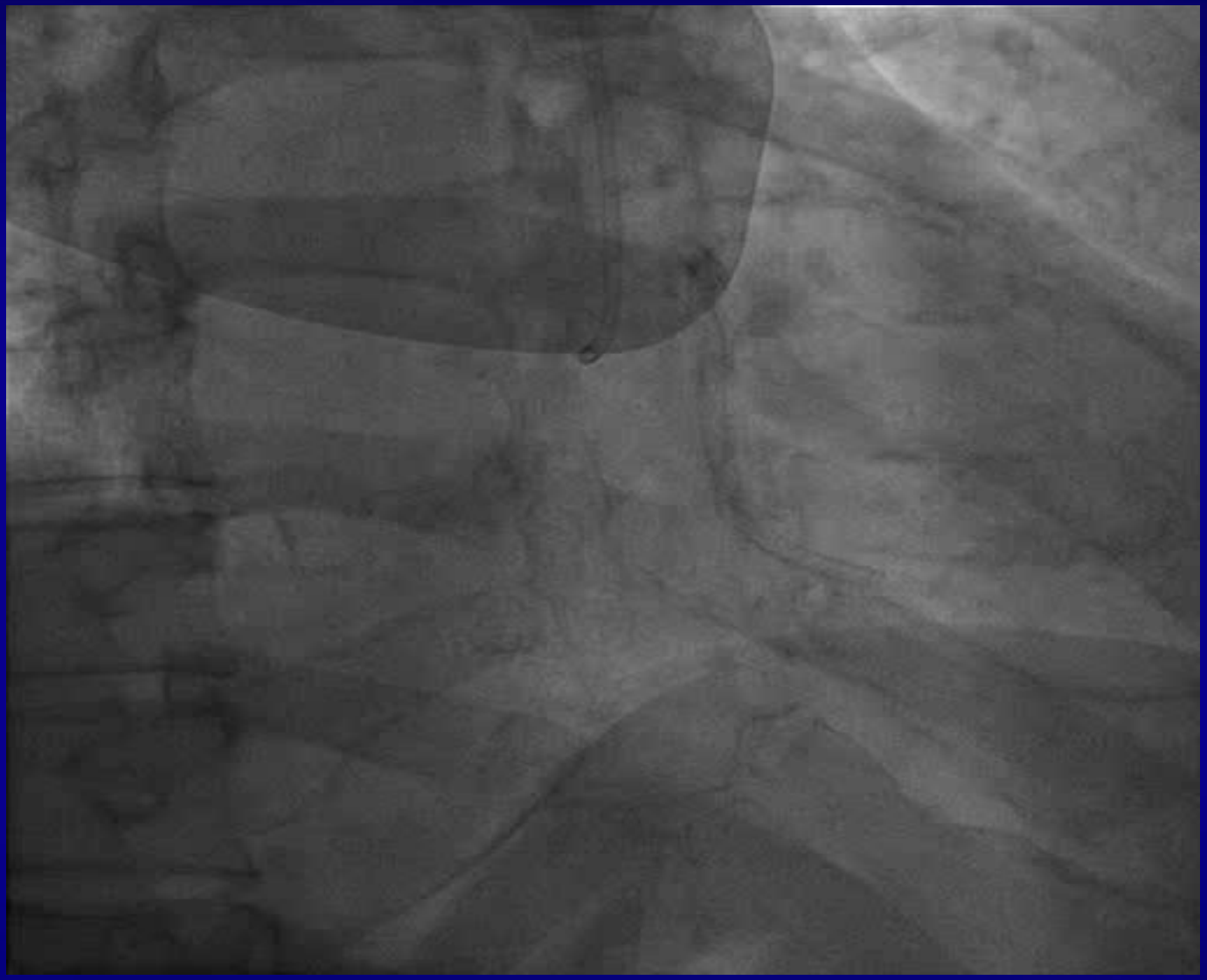
Hyperlipidemia **(46.1%)**
(LDL-C ≥100 mg/dL, TC ≥200 mg/dL, or TG ≥150 mg/dL)

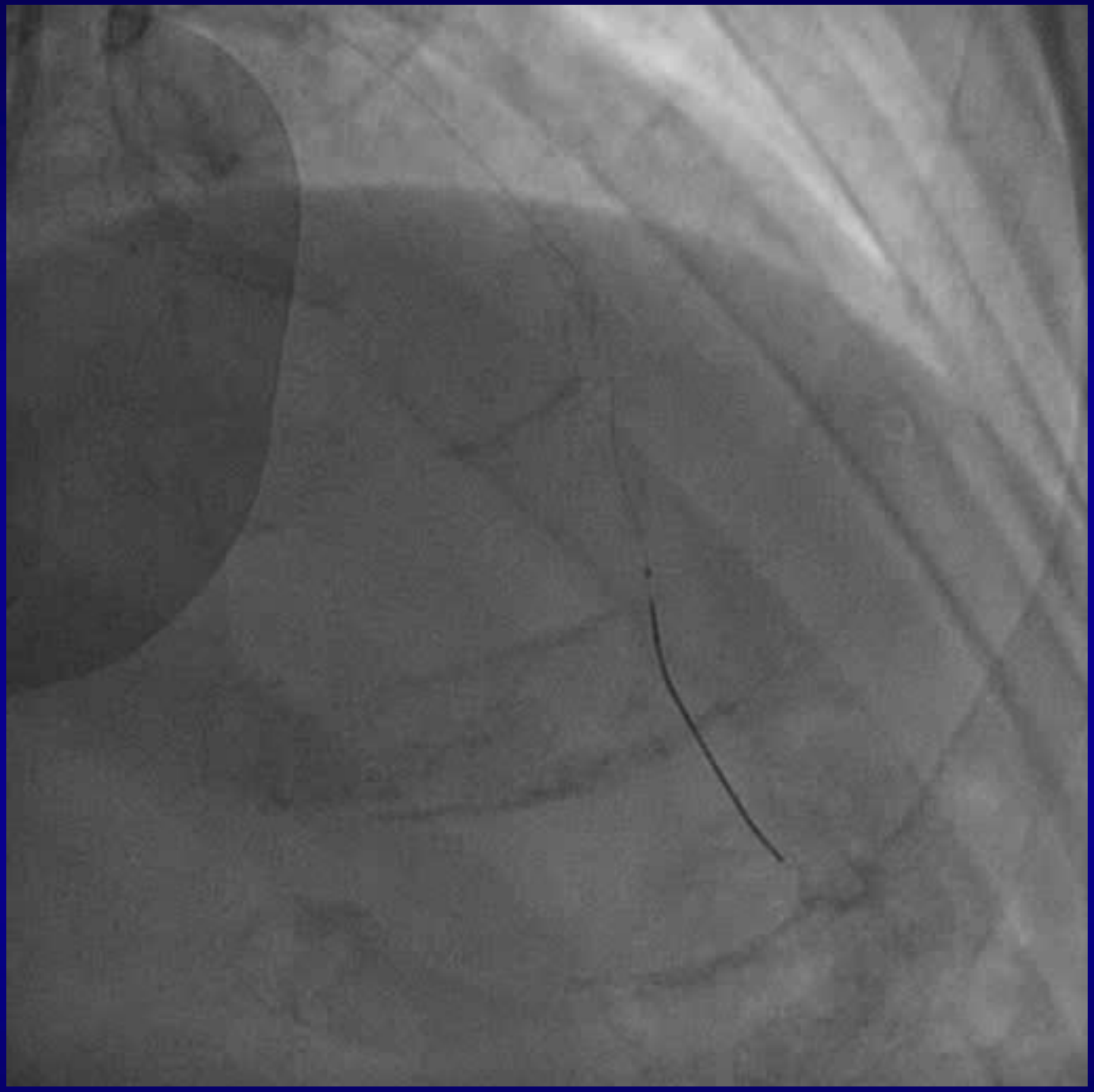
T2DM usually complicated by other medical conditions, only 14% of patients with type 2 diabetes had no other comorbidities

Suh DC, et al. J Diabetes Complications. 2010;24:382-391.

NHANES: National Health and Nutrition Examination Surveys

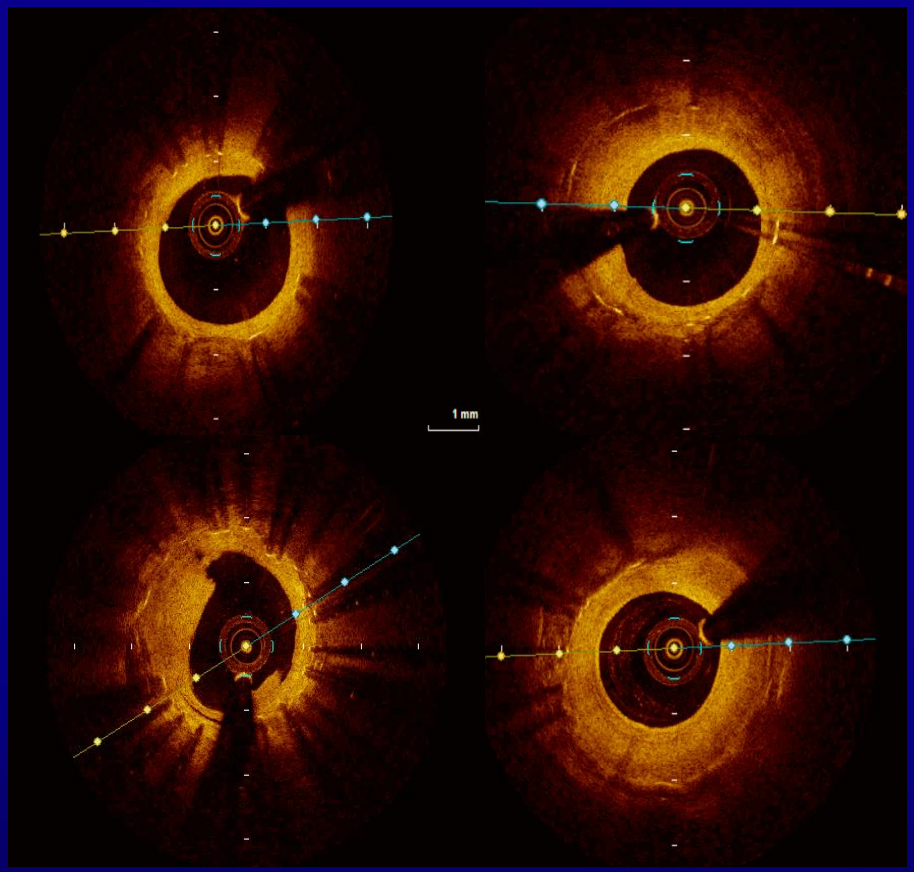




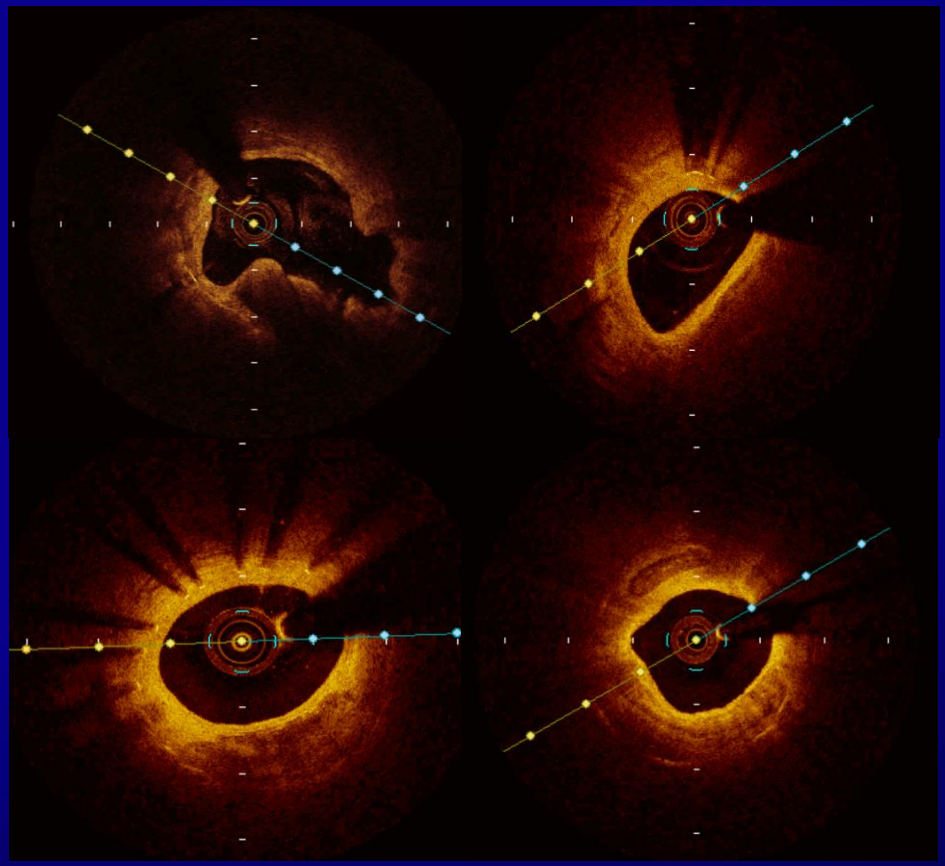


Neoatherosclerosis

Neoatherosclerosis (-)



Neoatherosclerosis (+)



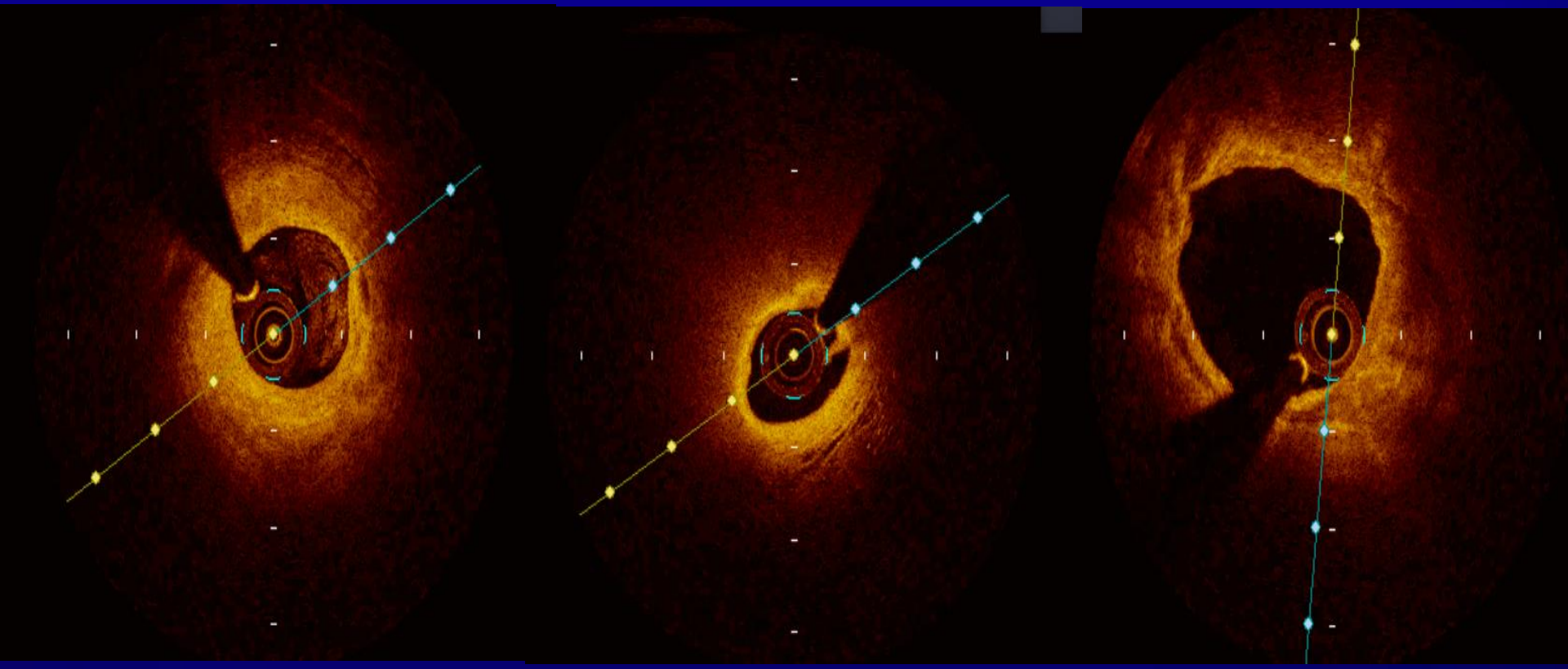
Int. J. Cardiol. 2019, 289;131-137

Plaque Classification

Fibrotic plaque

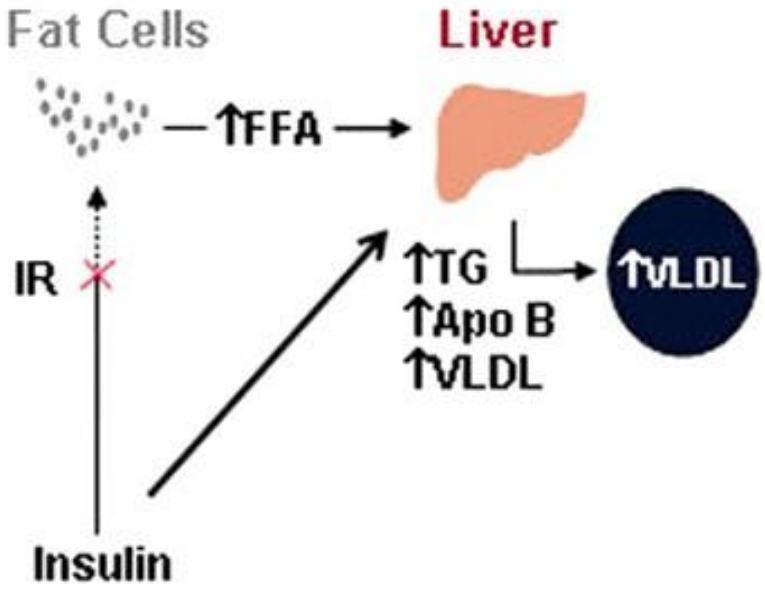
Fibrolipidic plaque

Fibrocalcified plaque



Atheroscloersis 2019, in press

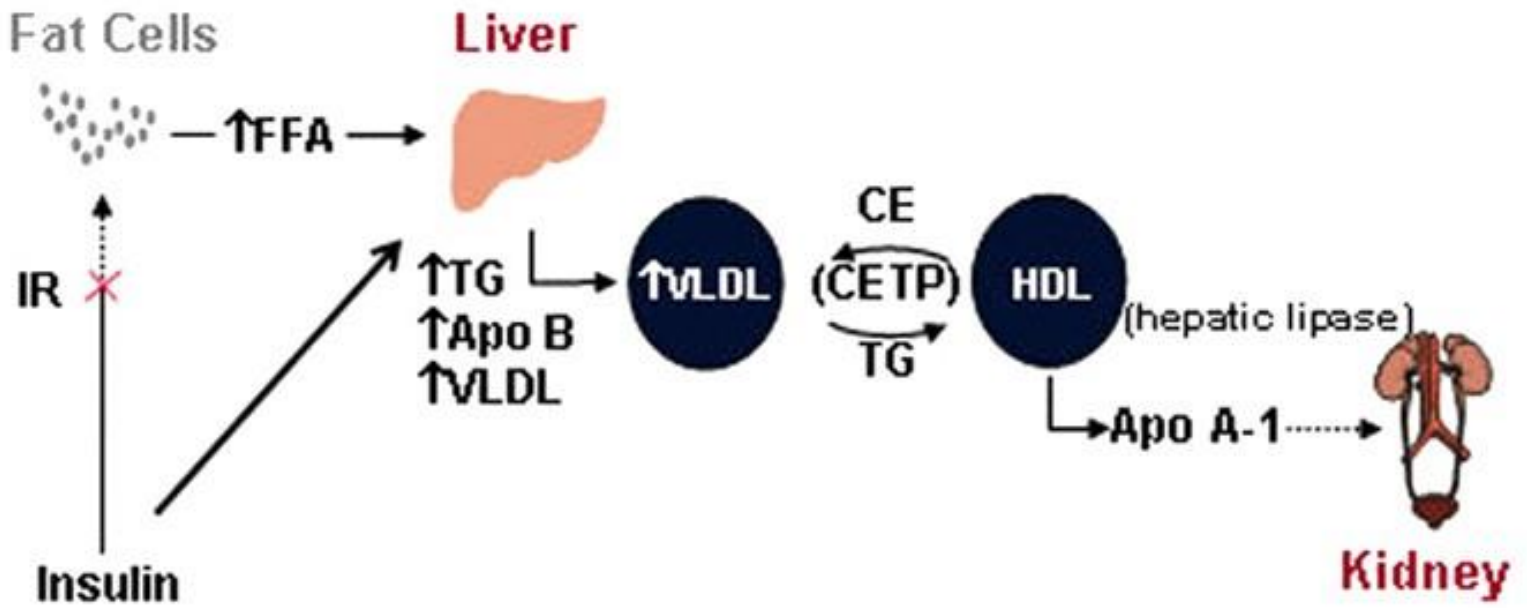
Diabetic Dyslipidemia



IR: Insulin Resistance CE, cholesteryl esters; FFA, free fatty acids; TG, triglycerides.
CETP: Cholesterol Ester Transport Protein

HN Ginsberg. J Clin invest. 2000;106:453-458

Diabetic Dyslipidemia



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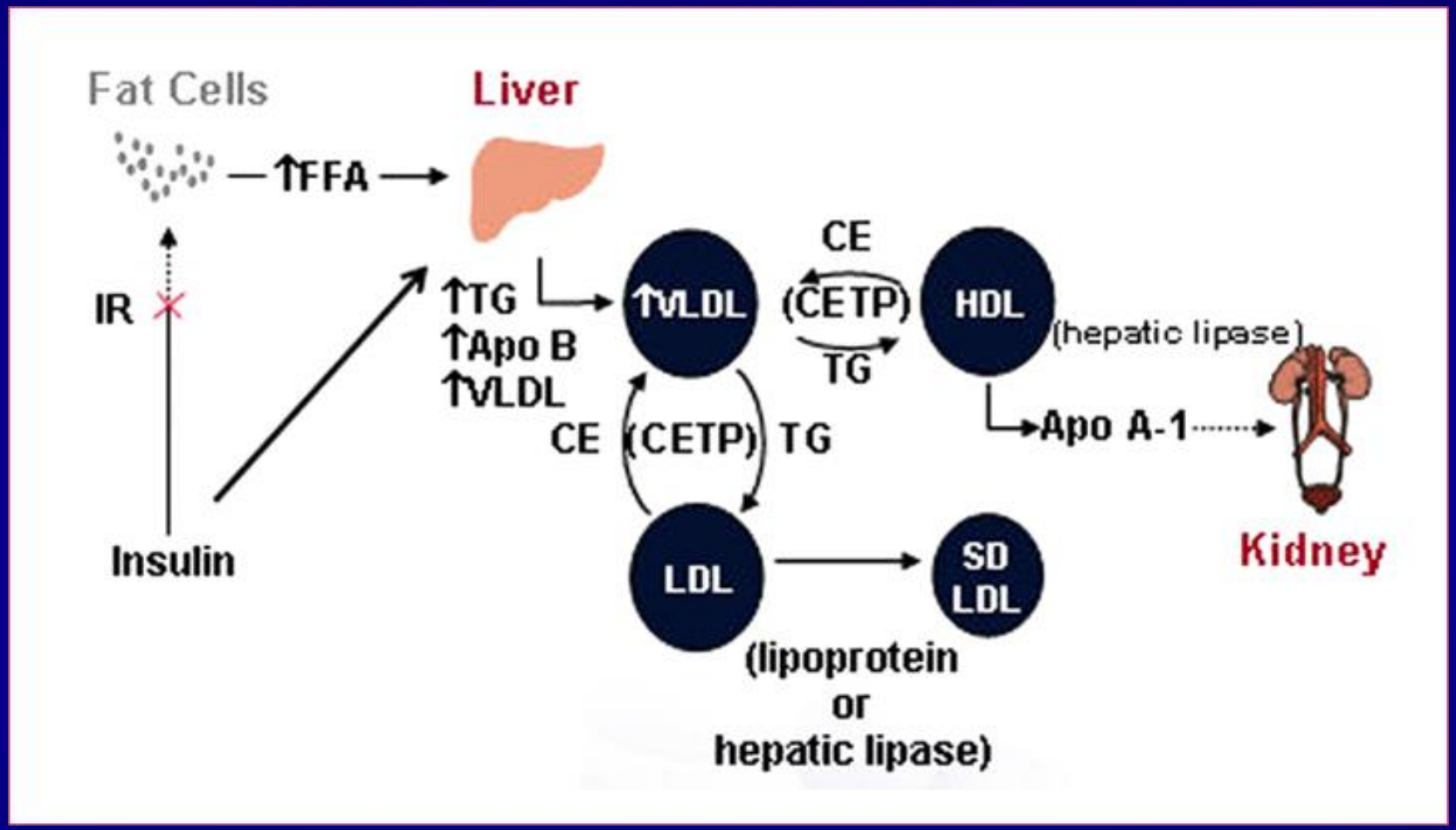
Diabetic Dyslipidemia



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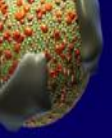
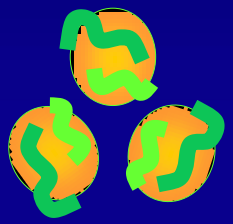
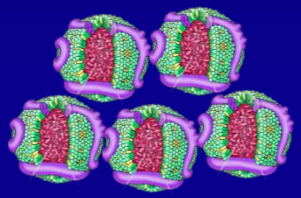
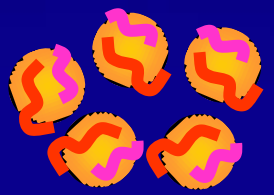
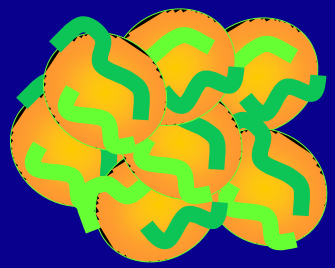
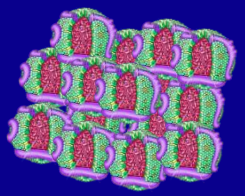
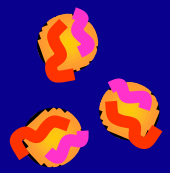
HN Ginsberg. J Clin invest. 2000;106:453-458

Dyslipidaemia of intra-abdominal obesity and T2DM

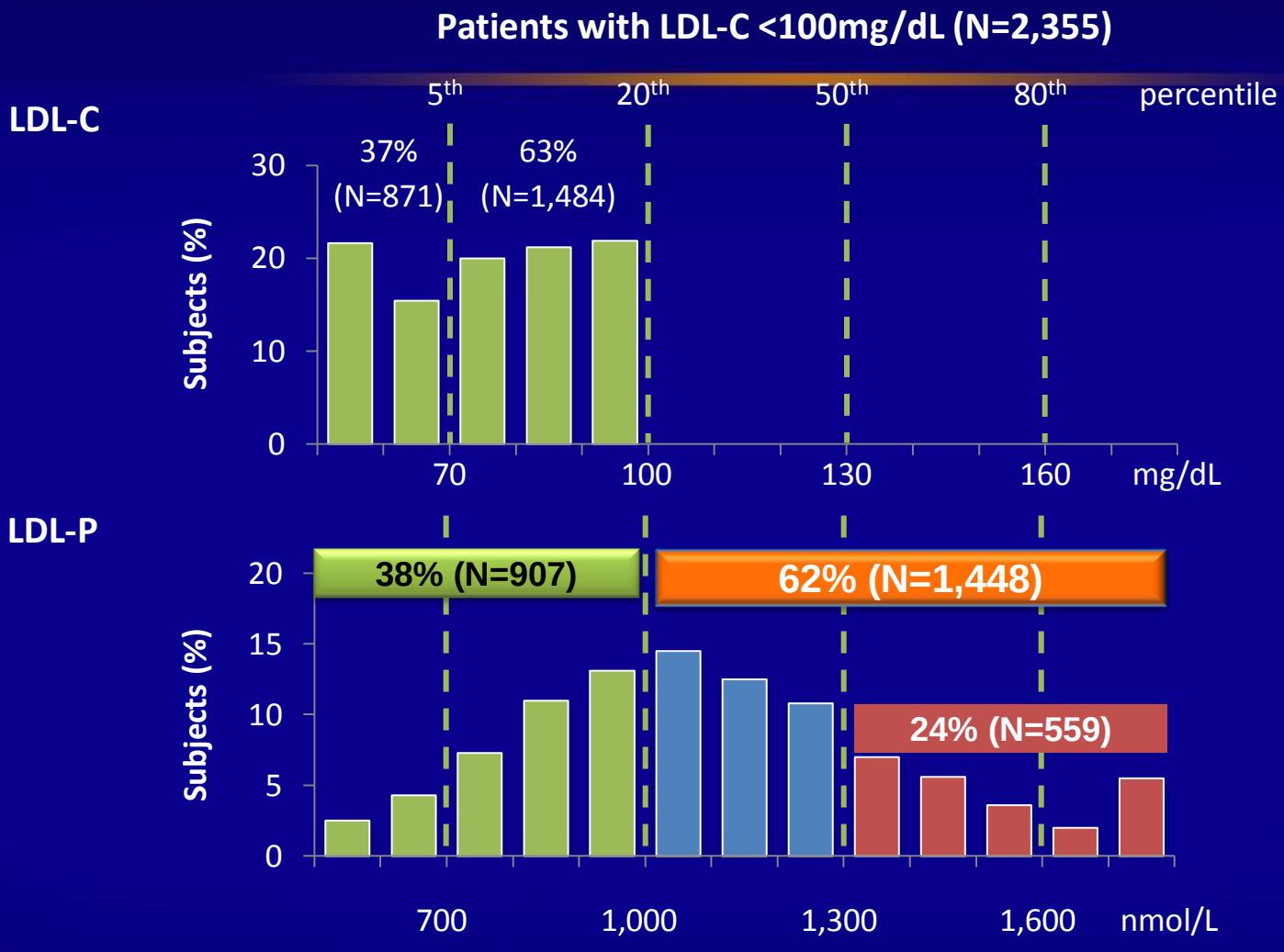


	VLDL	LDL	HDL
Normal			
Insulin resistance			
	↑ VLDL triglycerides ↑ VLDL apo B	↑ LDL apo B ↑ particle number ↓ particle size (small, dense)	↓ HDL cholesterol ↓ particle number ↓ particle size (small, dense)

VLDL: very low-density lipoprotein; LDL: low-density lipoprotein
HDL: high-density lipoprotein; Apo B: apolipoprotein B

Watts G. Diapedia 2014. Available at: http://www.diapedia.org/61040851150/rev/5.
Last accessed September 2016

LDL-C and LDL particle number in T2D

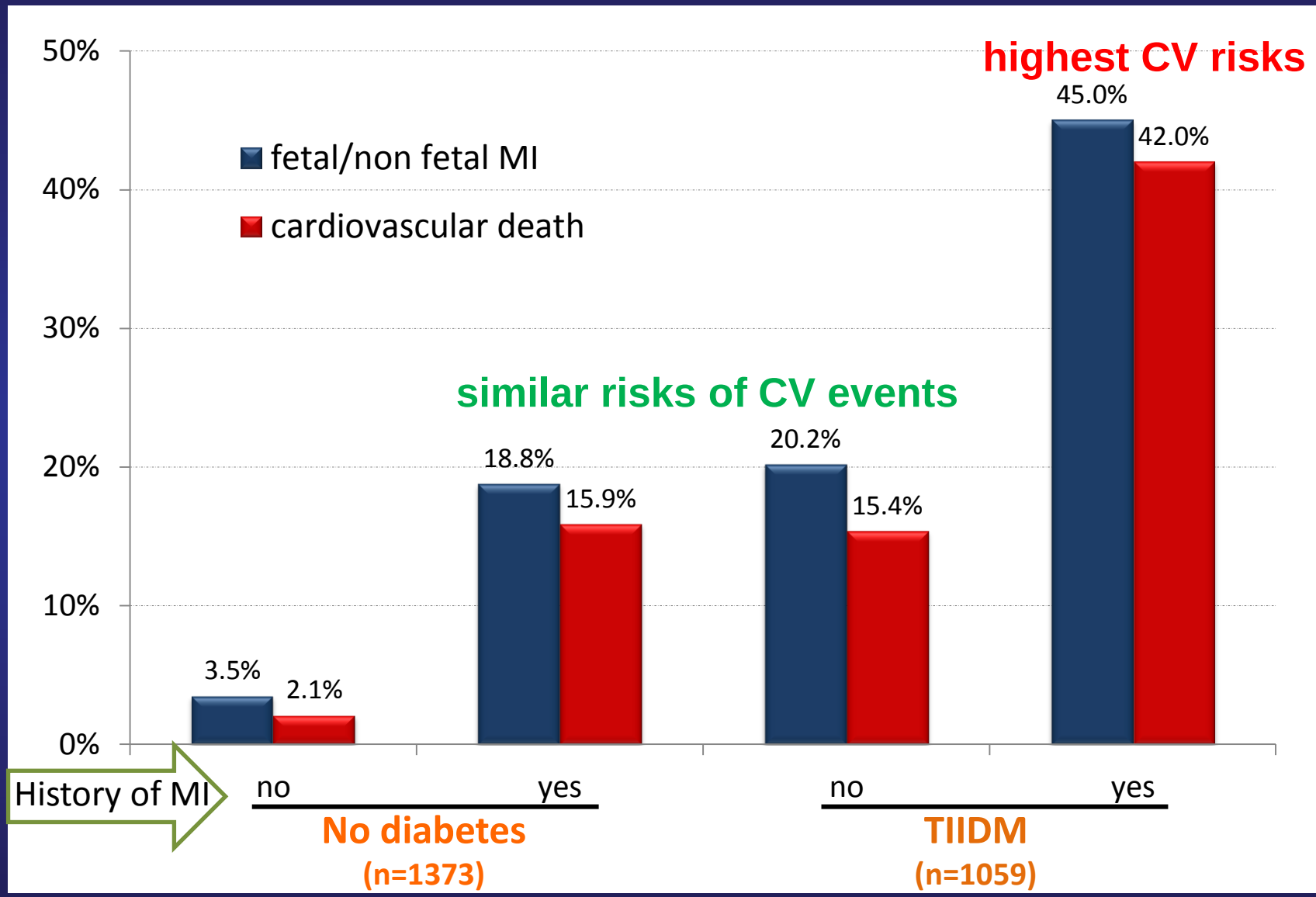


Discordance between LDL-C and LDL-P in patients with diabetes
62% at high risk (LDL-P >= 1,000) despite optimum LDL-C (<100mg/dL)

LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particles

Cromwell WC, Otvos JD Am J Cardiol. 2006;98:1599–1602

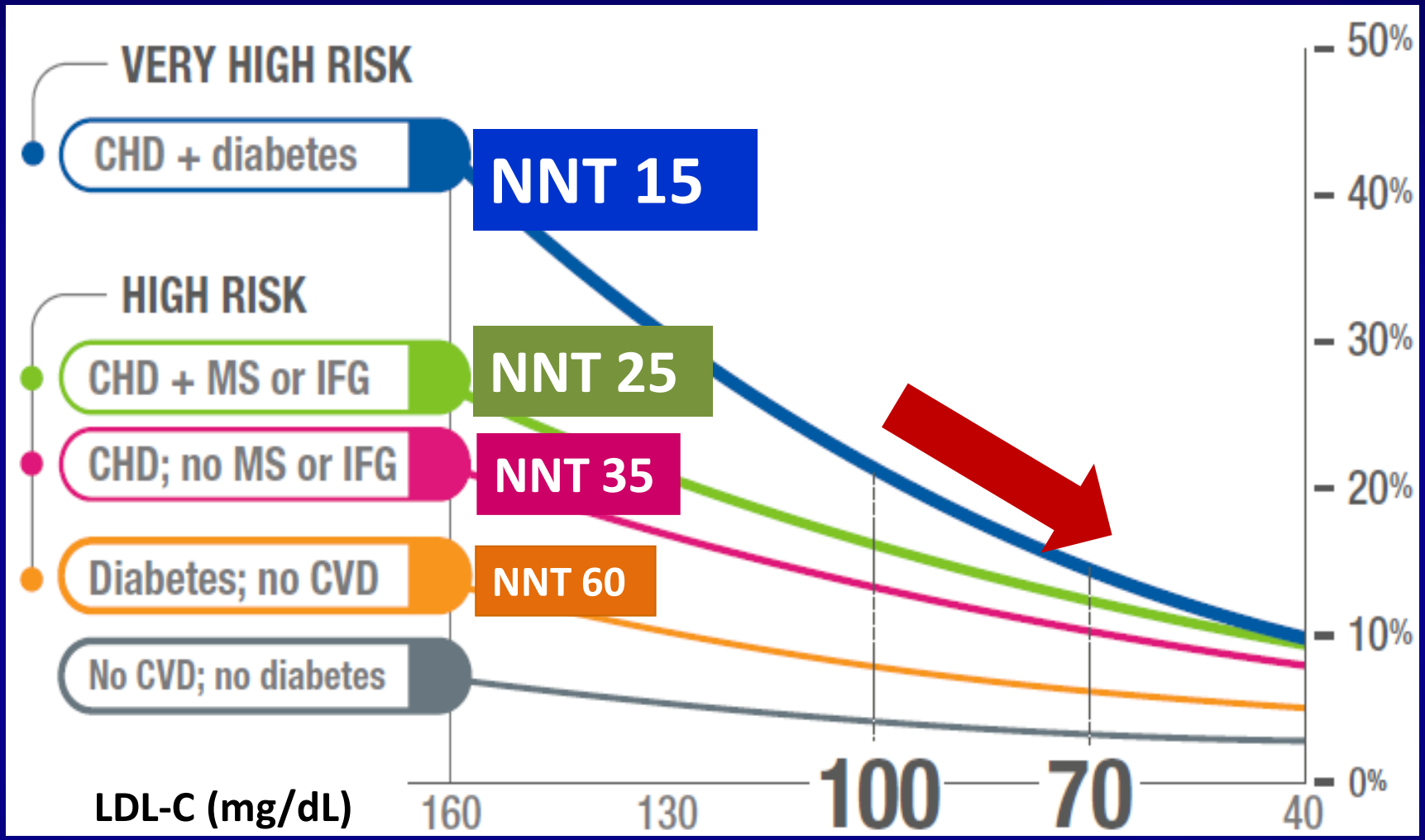
Diabetes and Myocardial Infarction History
Increased Incidence of Cardiovascular Events



7-year incidence of cardiovascular events in relation to diabetic status and history of myocardial infarction at baseline
$p < 0.001$ (for prior MI vs. no prior MI; for DM vs. no DM) TIIDM: TYPE 2 DIABETES; MI: Myocardial Infarction

N Engl J Med 1998;339:229-34.

Rate of CV Events Are Related to Risk Level and LDL-C



*5-year NNT to prevent 1 ASCVD event; NNT: # of risk patients needed to be treated to prevent one event over 5 years

Intent-to-treat LDL cholesterol level and risk for hard cardiovascular events (nonfatal MI, CHD death, and stroke) by the presence of CHD, metabolic syndrome (MS), impaired fasting glucose (IFG), or diabetes in placebo-controlled statin trials of approximately 5 years in duration

Robinson JG and Stone NJ. *Am J Cardiol*. 2006;98:1405–1408; Robinson JG. Curr Cardiol Rep. 2008;10:481–7.

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017

TASK FORCE

Alan J. Garber, MD, PhD, FACE, *Chair*

Martin J. Abrahamson, MD
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Guillermo Umpierrez, MD, FACP, FACE

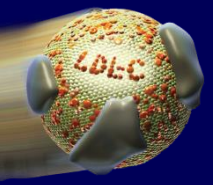
 DOI 10.4158/EP161682.CS

ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – **Established clinical cardiovascular disease in individuals with DM**, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	**<55**	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – **DM** or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	**<70**	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

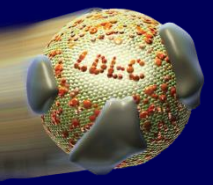
Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation.* 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.



2017 Taiwan Lipid Guidelines for High Risk Patients: Lipid Recommendations for Diabetic Patients

Recommended Target	Individuals who should be targeted for lipid modification	Risk assessment algorithm
LDL-C: - **Without CVD: < 100 mg/dL** - **With CVD: < 70 mg/dL or 30-40% reduction** - **TG < 150 mg/dL** **HDL-C:** - **Men: > 40 mg/dL** - **Women > 50 mg/dL**	1. All diabetic patients aged ≥ 40 years 2. Diabetic patients aged < 40 years who have overt ASCVD or ASCVD risk factors	ASCVD risk factors include: - High blood pressure - Smoking - Overweight and obesity - Family history of premature ASCVD

Li Y-H, et al., 2017 Taiwan lipid guidelines for high risk patients, Journal of the Formosan Medical Association (2016), http://dx.doi.org/10.1016/j.jfma.2016.11.013

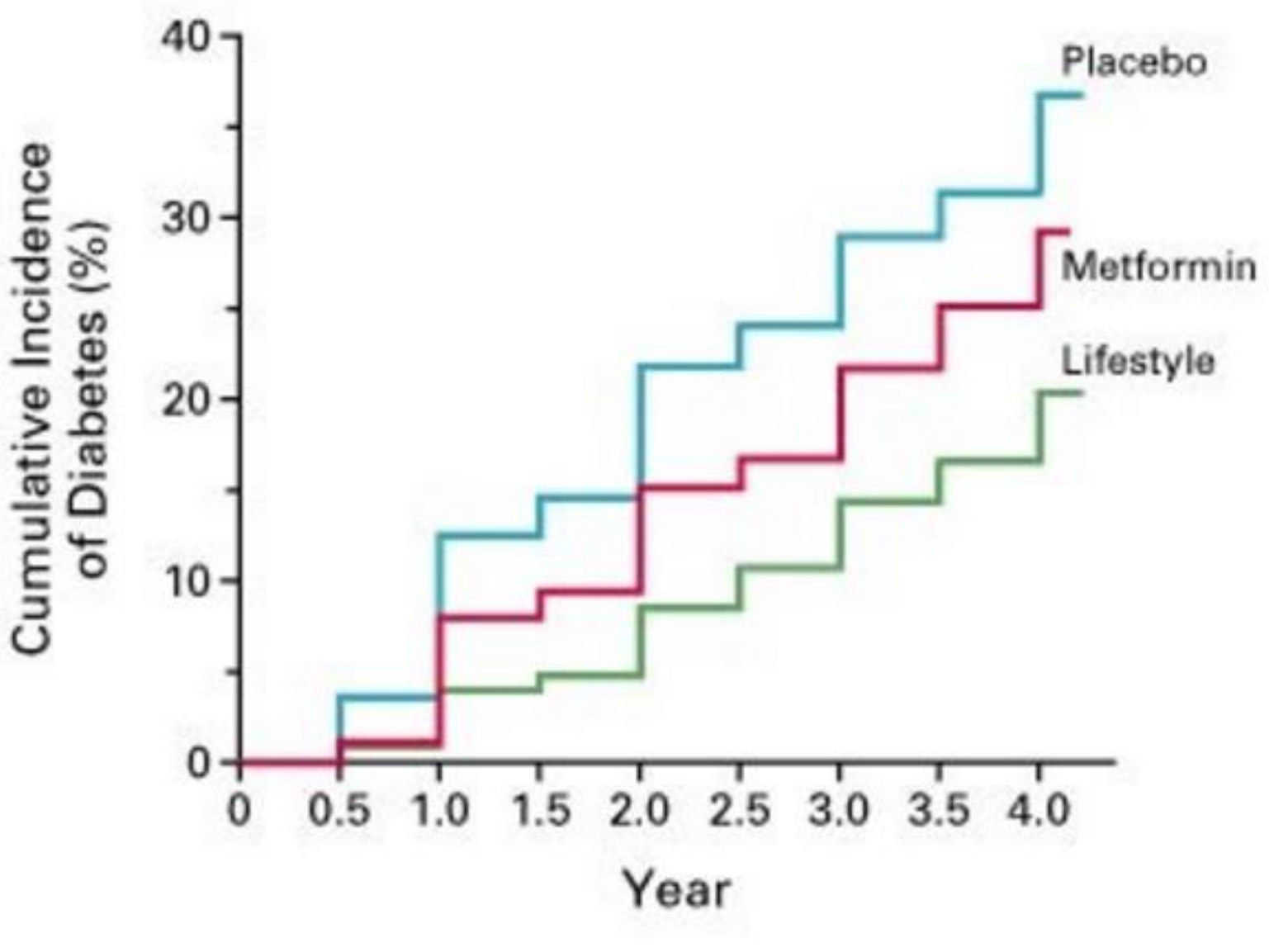


2017-台灣高風險病人血脂異常治療指引 LDL-C治療目標

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 小孩: < 135 mg/dL 有心血管疾病: < 70 mg/dL

J Formos Med Assoc. 2017 Feb 24.

Lipid Lowering Strategy



Lifestyle Intervention

1. **Intensive diet counseling program**
   - reducing saturated fat, cholesterol, and trans fat intake and increasing omega-3 fatty acids, plant sterols, and dietary fiber
2. **Increasing moderate-intensity physical activity**
   - Moderate-intensity physical activity (such as brisk walk) for a minimum of 150 min/ wk
3. **Targeting a loss of 7% of body weight in obese individuals.**

Table 4 Healthy lifestyle recommendations.

Lifestyle change	Recommendation
Sodium restriction	2.0—4.0 gm/d
Alcohol limitation	Men: <30 gm/d ethanol Women: <20 gm/d ethanol
Body weight reduction	BMI: 22.5—25.0
Cigarette smoking cessation	Complete abstinence
Diet adaptation	DASH diet: rich in fruits and vegetables (8—10 servings/d), rich in low-fat dairy products (2—3 servings/d), and reduced in saturated fat and cholesterol
Exercise adoption	Aerobic, at least 40 min/d, and at least 3—4 d/wk

BMI = body mass index; DASH = Dietary Approaches to Stop Hypertension.

Note. From "2015 guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the management of hypertension," by C.E. Chiang, T.D. Wang, K.C. Ueng, T.H. Lin, H.I. Yeh, C.Y. Chen CY et al, 2015, *J Chin Med Assoc*, *78*, p. 1—47. Copyright 2017, *Journal of the Chinese Medical Association*. Adapted with permission.

Lipid Lowering Strategy

Diet

Statin

Ezetimibe

Table 5 Summary of lipid-lowering drugs.

Drug class	Agents and daily doses	Lipid/lipoprotein effects	Side effects	Other considerations
Statins	Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–40 mg) Fluvastatin (20–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (5–40 mg) Pitavastatin (1–4 mg)	LDL ↓ 20–60% HDL ↑ 5–15% TG ↓ 7–30% Non-HDL ↓ 15–50%	Myalgia Myositis Increased serum transaminases	Rare rhabdomyolysis Cognitive decline New-onset diabetes
Cholesterol absorption inhibitor	Ezetimibe 10 mg	LDL ↓ 15–22% HDL ↑ 1–2% TG ↓ 5–10% Non-HDL ↓ 14–19%	Headache Muscle pain	Effective in combination with statin
PCSK9 inhibitors	Evolocumab (140 mg, s.c., Q2W) Alirocumab (75 mg, s.c., Q2W)	LDL ↓ 50–70% HDL ↑ 4–7% TG ↓ 6–19% Non-HDL ↓ 20–50%	Injection site reaction (5%)	Not increased serum transaminases Require subcutaneous injection
Nicotinic acid	IR nicotinic acid (1.5–3 g) ER nicotinic acid (1–2g) SR nicotinic acid (1–2 g)	LDL ↓ 15–18% HDL ↑ ~25% TG ↓ 20–40% Non-HDL ↓ 8–23%	Flushing Hyperglycemia Hyperuricemia GI distress Hepatotoxicity Excess infection	Glucose intolerance ER niacin more tolerable than IR
Fibric acids	Gemfibrozil, 600 mg bid Bezafibrate, 200 mg bid/tid Fenofibrate, 200 mg qd Fenofibric acid, 135 mg qd	LDL ↓ 10-15% HDL ↑10-20% TG ↓ 20-50% Non-HDL ↓ 5-19%	Dyspepsia Increased serum transaminases Gallstones Myopathy	May ↑ creatinine + homocysteine Do not combine gemfibrozil + statin
Omega-3 fatty acids	Omega-3 fatty acids 2–4 g	LDL ↓6%–↑25% HDL ↓5%–↑7% TG ↓ 20–45% Non-HDL ↓ 5–14%	Fishy smell Skin eruption	Combination with statin improve postprandial TG level

ER = extended-release; HDL-C = high-density lipoprotein cholesterol; IR = immediate-release; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SR = sustained-release; s.c. = subcutaneous; TG = triglyceride.

Table 6 Intensity of statin therapy.

High-intensity statins daily dosage ↓ LDL-C ≥ 50%	Moderate-intensity statins daily dosage ↓ LDL-C 30% to <50%
Atorvastatin, 40—80 mg	Atorvastatin, 10—20 mg
Rosuvastatin, 20—40 mg[a]	Fluvastatin XL, 80 mg
	Lovastatin, 40 mg
	Pitavastatin, 2—4 mg
	Pravastatin, 40—80 mg
	Rosuvastatin, 5—10 mg
	Simvastatin, 20—40 mg

LDL-C = low-density lipoprotein cholesterol.

[a] The maximal dose approved for rosuvastain in Taiwan is 20 mg once daily. The 40 mg dose of rosuvastatin is reserved only for those patients who have familial hypercholesterolemia (FH).

Recommendation

- Ezetimibe alone can be considered an alternative to statins in patients who have statin contraindications or intolerance. (COR IIa, LOE C)
- Ezetimibe can be used in combination with statins when the therapeutic target is not achieved at maximal tolerated statin dose. (COR IIa, LOE B)
- For patients with ACS, routine use of the moderate intensity statin combined with ezetimibe may be an alternative. (COR IIa, LOE B)

Lipid Lowering Strategy

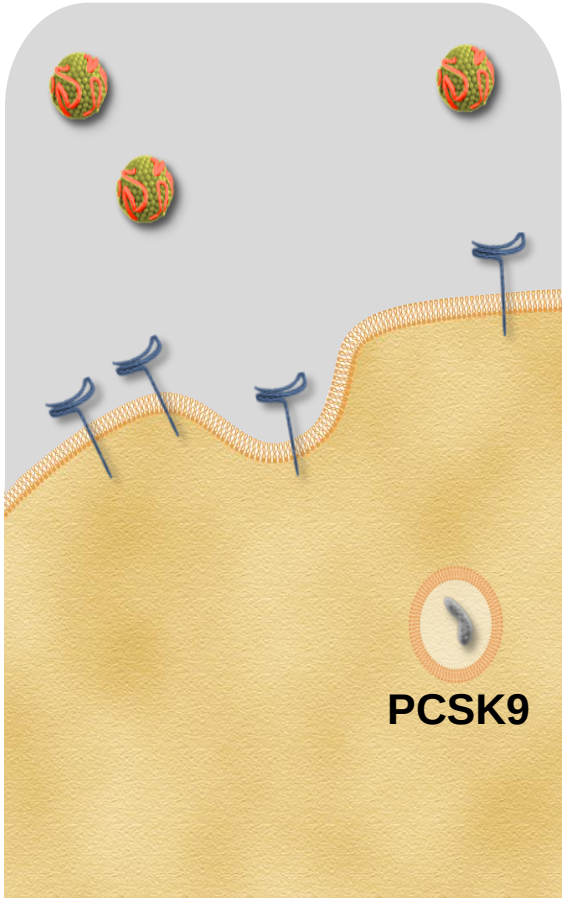
Diet

Statin

Ezetimibe

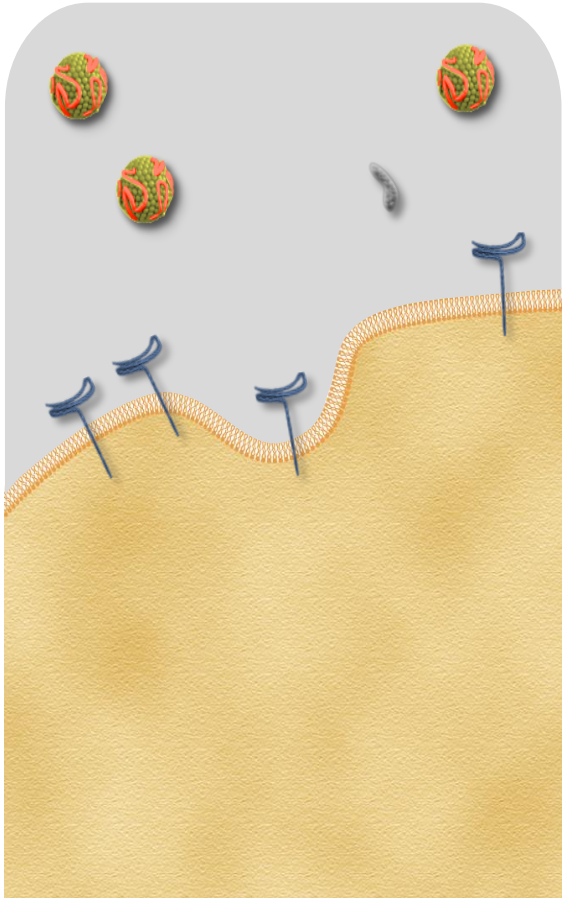
PCSK9 inhibitor

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



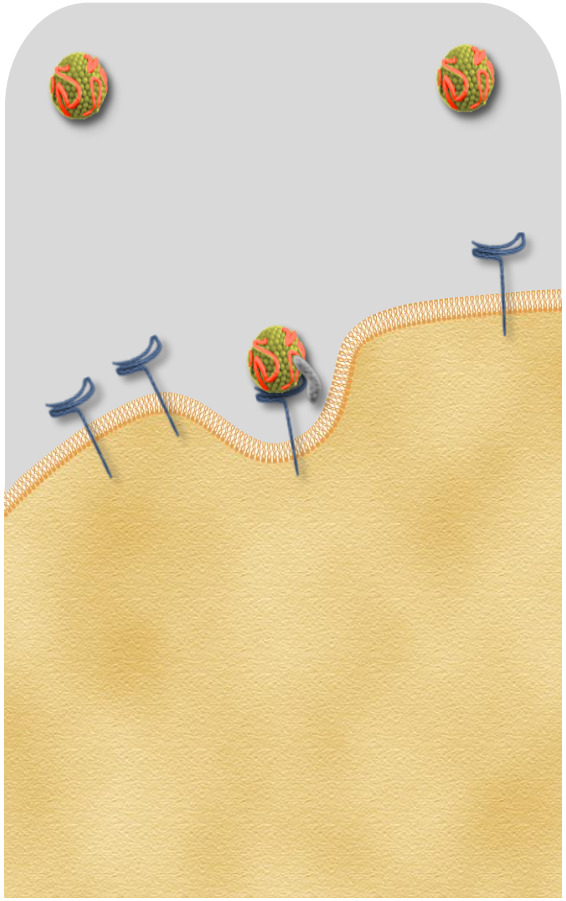
- plays an important role in the regulation of plasma levels of atherogenic LDL-C
- PCSK9 is primarily expressed in the liver

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



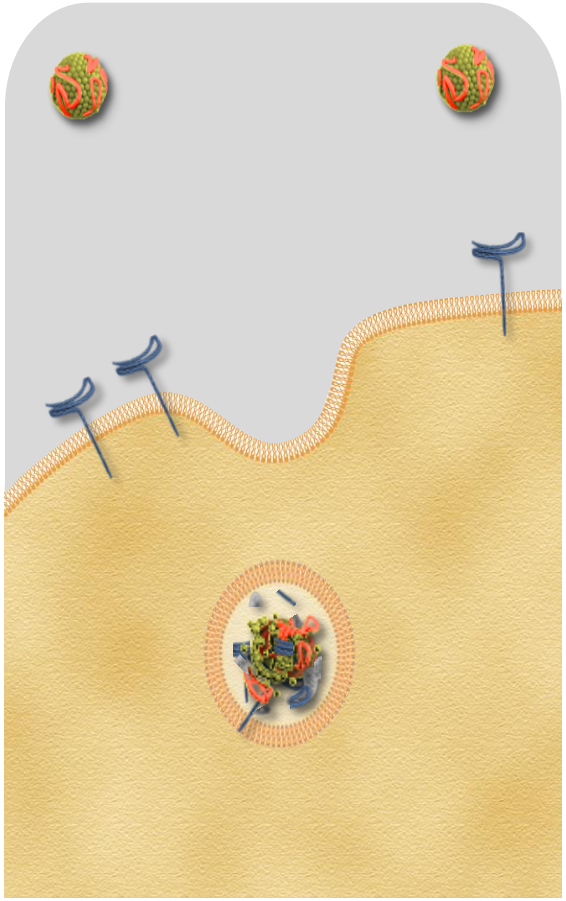
- Following secretion, PCSK9 binds to the LDL receptor[1,2]
- The LDL receptor is the primary receptor that clears circulating LDL

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



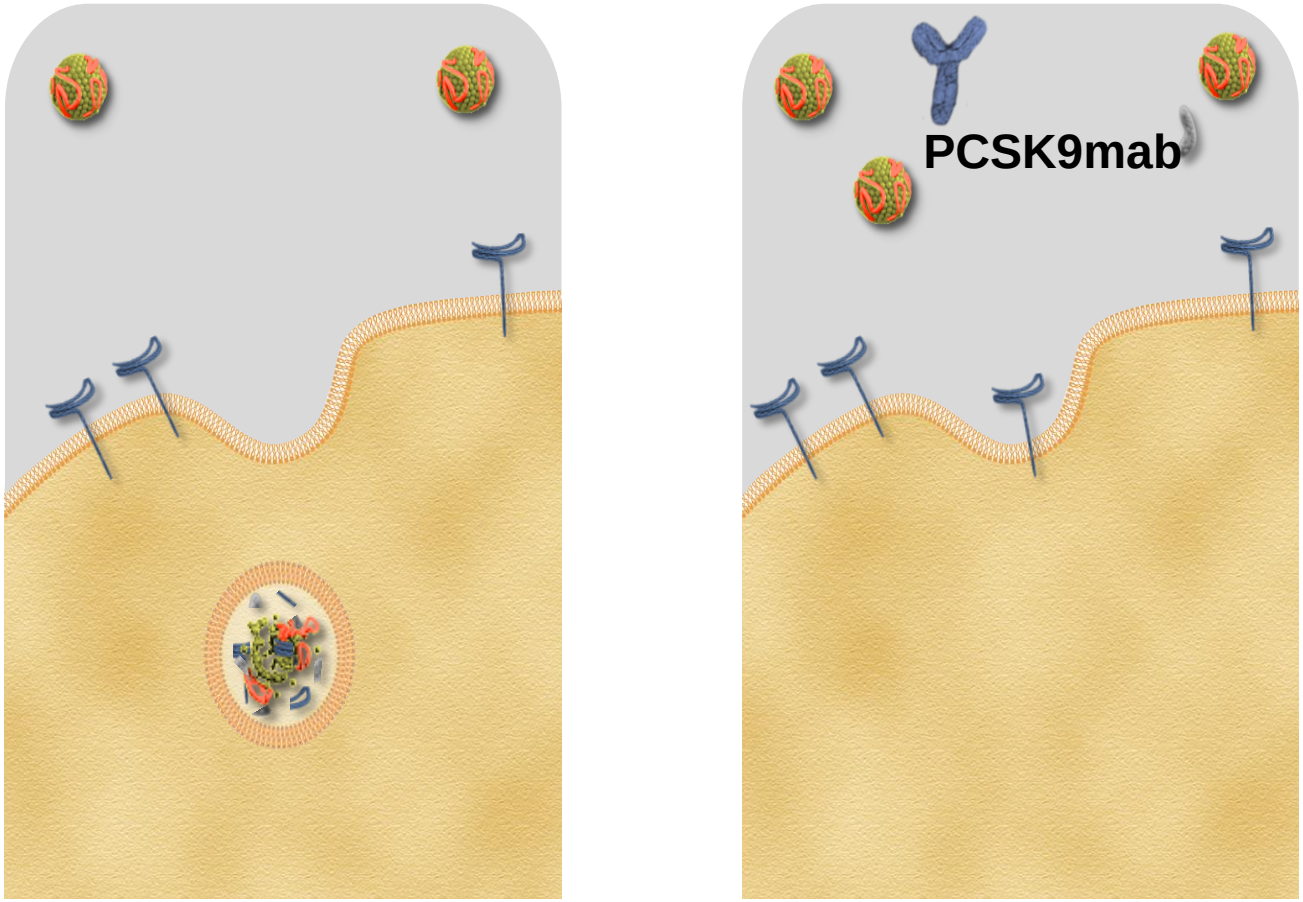
- The binding of LDL to the LDL receptor results in internalization of the receptor, LDL, and PCSK9

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



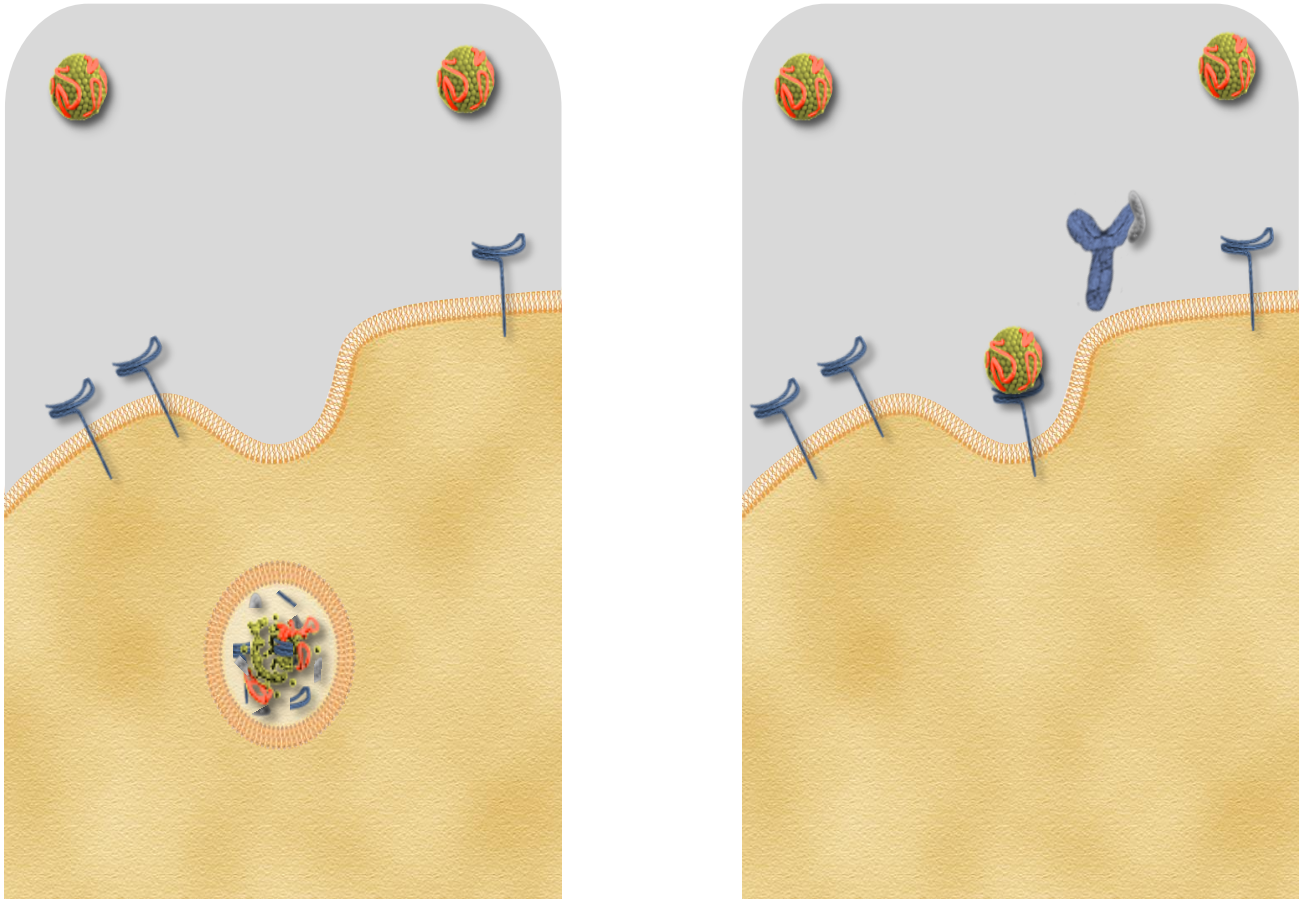
- The presence of PCSK9 leads to increased LDL receptor degradation

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



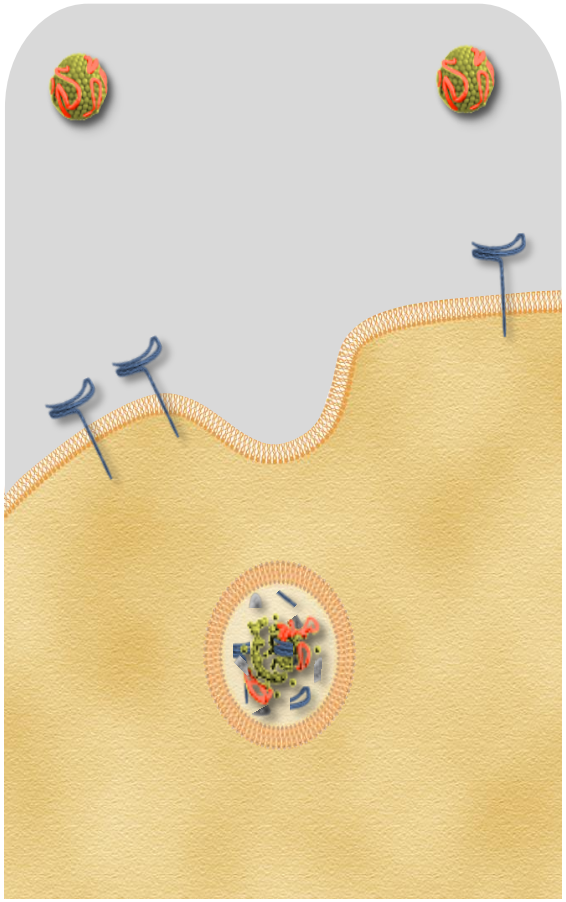
- PCSK9mab binds to PCSK9, preventing PCSK9 from binding to the LDL receptor

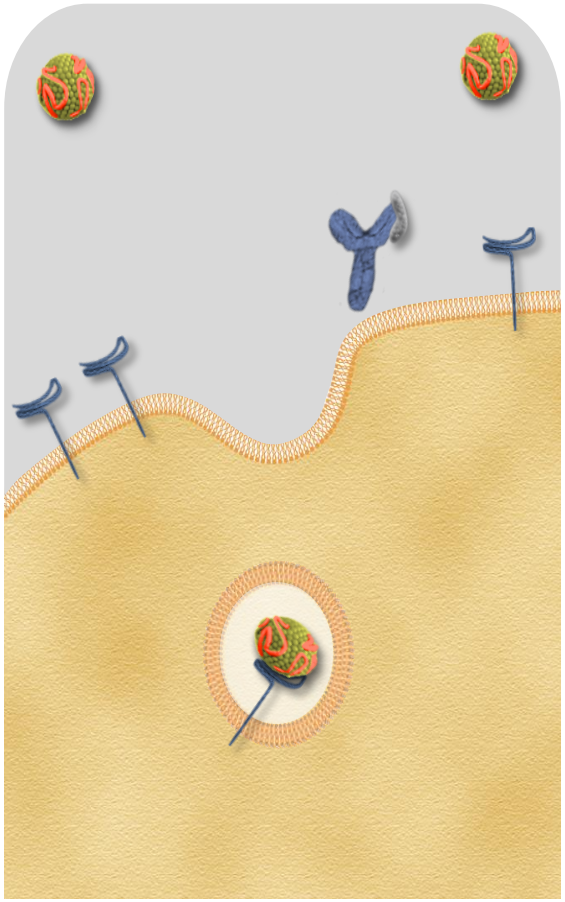
PCSK9 Physiology and Inhibition by PCSK9 mab Injection



- LDL binds to the receptor in the absence of PCSK9. The complex of “only” the receptor and LDL (ie, no PCSK9) is then internalized into clathrin-coated vesicles by endocytosis[1,2]

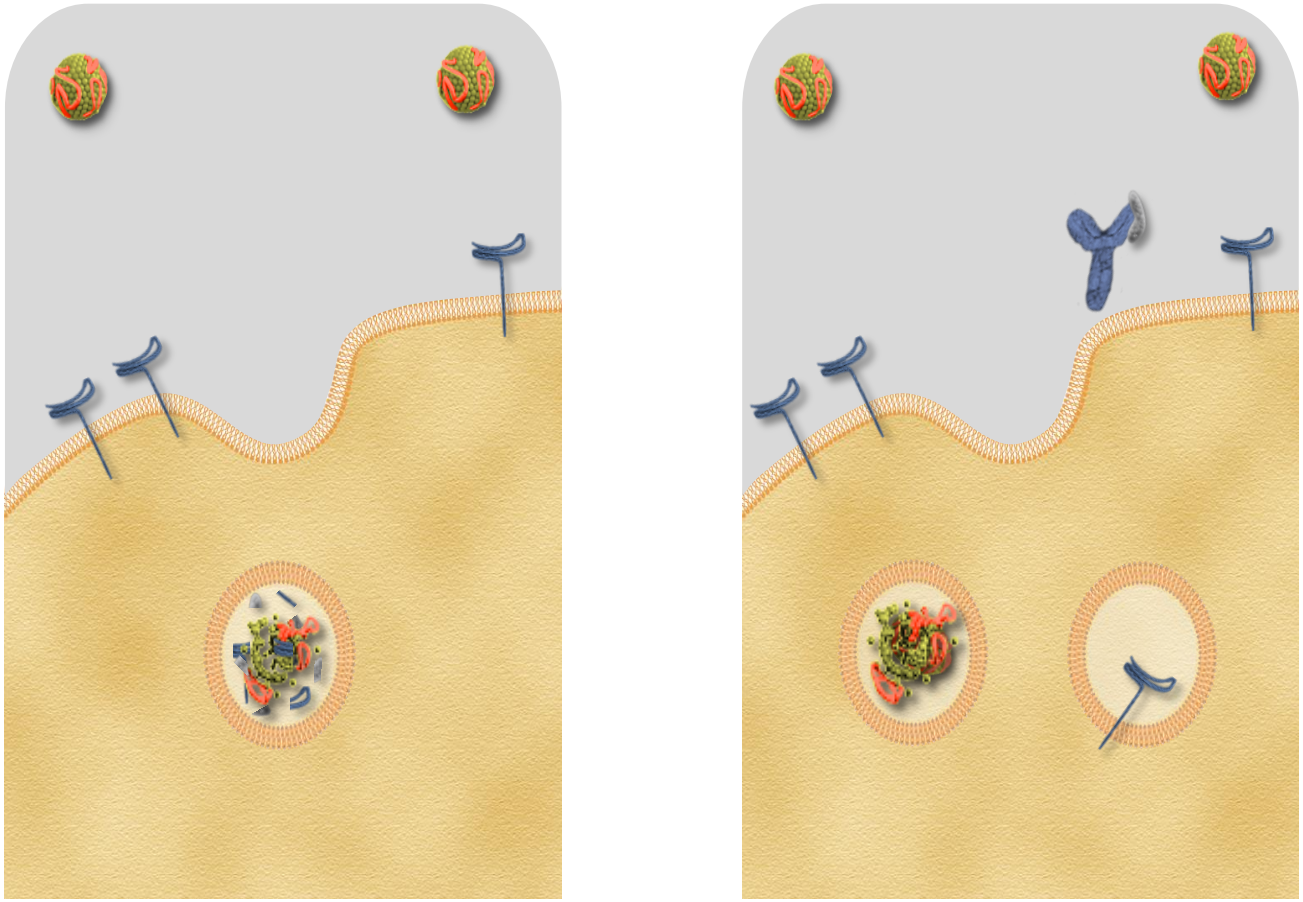
PCSK9 Physiology and Inhibition by PCSK9 mab Injection





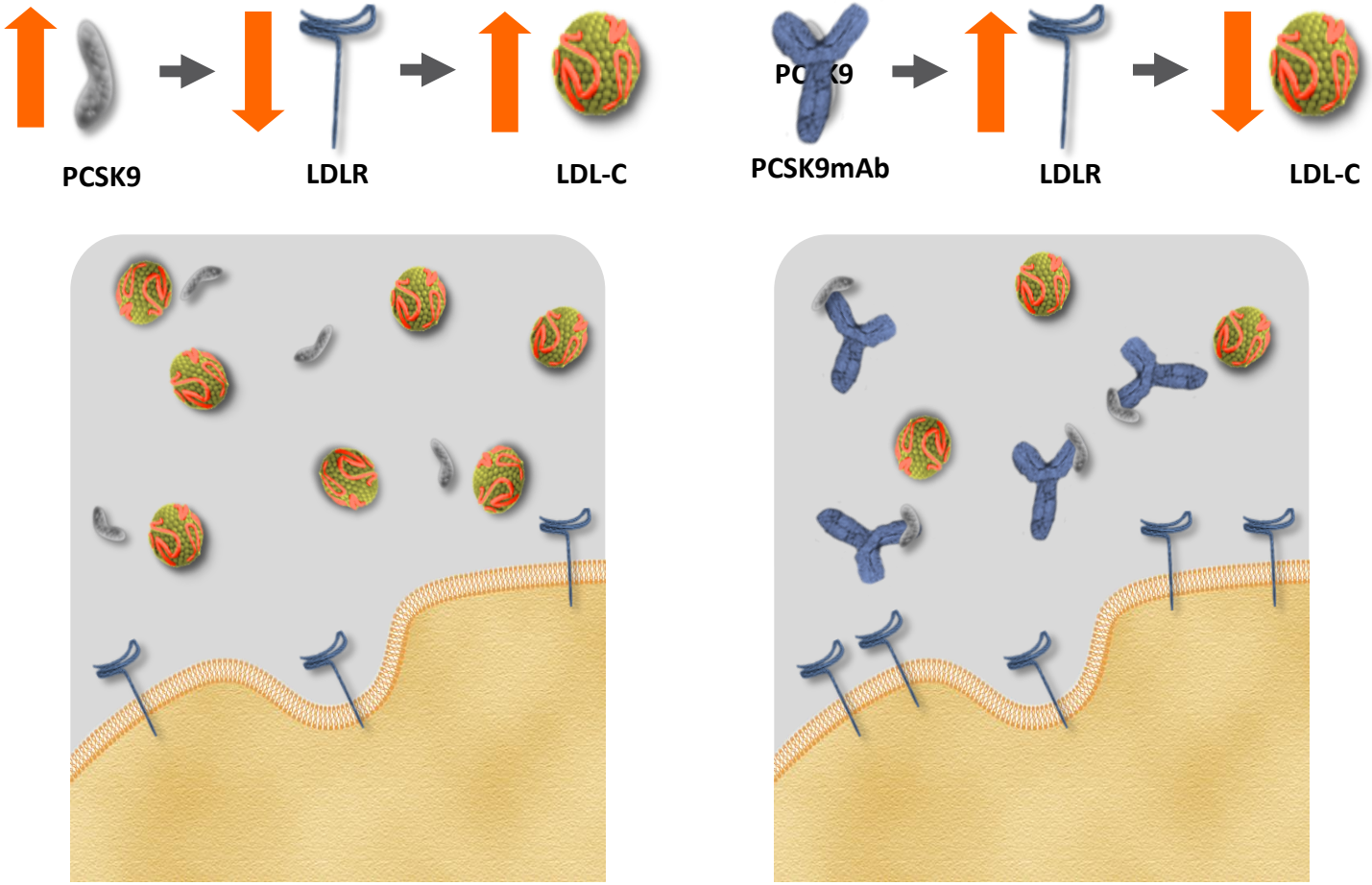
- LDL then separates from its receptor

PCSK9 Physiology and Inhibition by PCSK9 mab Injection



- The LDL receptor is then recycled to the cell surface for reuse[1]
- At the same time, LDL is degraded[2]

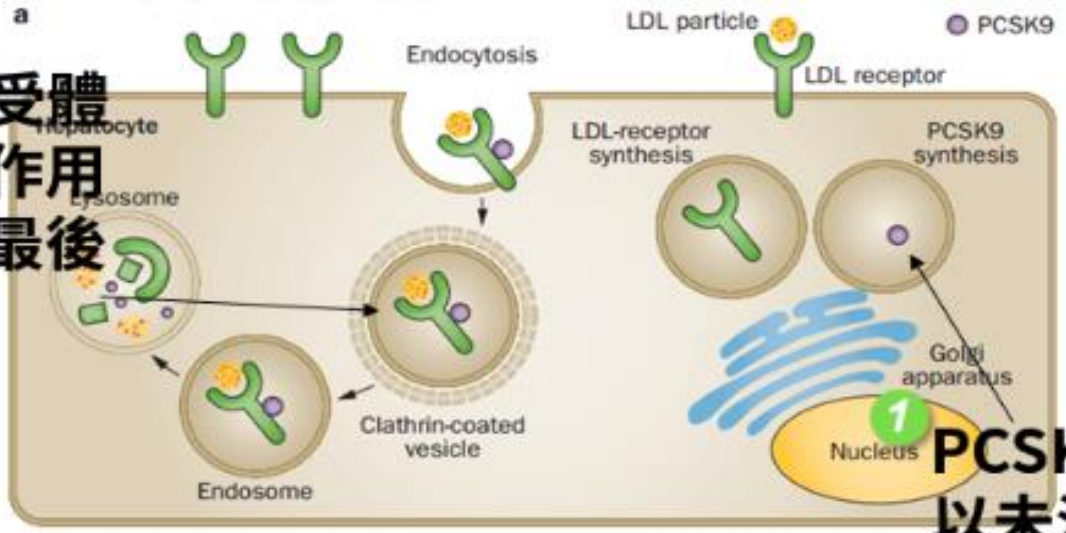
PCSK9 Physiology and Inhibition by PCSK9 mab Injection



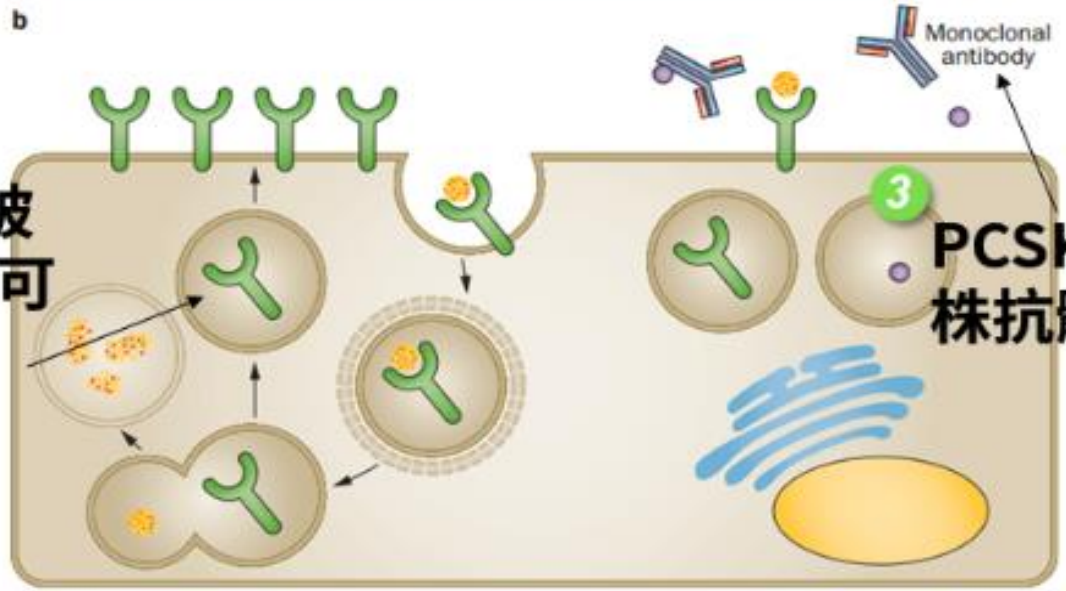
LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9.

PCSK9 Physiology and Inhibition by PCSK9 mab Injection

2 PCSK9與LDL受體結合，經胞噬作用進入肝細胞，最後被分解掉



1 PCSK9在肝臟製造以未活化態存在



3 PCSK9抑制劑 (單株抗體) 抓PCSK9

4 LDL受體避免被PCSK9抓走，可重複回收LDL

資料來源: Nat Rev Cardiol. 2014;11:563-75.

	FOURIER	ODYSSEY OUTCOMES
Population	Stable ASCVD	Recent ACS
Qualifying LDL-C, mg/dL	≥70	≥70
Primary endpoint	5-point MACE: CV death, MI, CVA, UA, coronary revasc.	4-point MACE: CHD death, MI, CVA, UA
Follow up	26 months	34 months
Age (median, years)	63	58
ACS <1 year	20%	100%
High-intensity statin	69%	89%
No statin	0.2%	2.5%

Outcomes relative risk reduction	FOURIER	ODYSSEY OUTCOMES
Primary endpoint	15%	15%
MI	27%	14%
Stroke	21%	27%
Unstable angina	1%	39%
CV death	+5% increase (NS)	12% (NS)
All cause death	+4% increase (NS)	15% (p=0.026*)

*Nominal P-value

Key patient populations may need additional LDL-C lowering therapies

Patients who could benefit from additional lipid lowering therapy	Magnitude of impact
High-risk patients with poorly controlled LDL-C despite treatment with standard of care[1]	Up to **76%** of high risk patients fail to reach their LDL-C goal of less than 70mg/dL[1]
Those who **cannot or will not take statins** due to adverse effects[2,3]	**10–20%** of patients treated with high dose statins show some degree of statin intolerance[2,7,8] **40–50%** of patients are non-adherent at 1 year[9,10]
Familial hypercholesterolemia • at high risk of premature coronary disease[4] and who fail to reach their LDL-C goal[5,6]	**Approximately 80%** of patients with familial hypercholesterolemia failed to reach an LDL-C target <100mg/dL[11]

1. Jones PH, et al. J Am Heart Assoc. 2012;1:e001800. doi: 10.1161/JAHA.112.001800. **2.** Bruckert E, et al. Cardiovasc Drugs Ther. 2005;19(6):403–14. **3.** Cohen JD, et al. J Clin Lipidol. 2012;6:208–15. **4.** Rees A. Eur Heart J. 2008;29:2583–4. **5.** Stein EA, et al. Am J Cardiol. 2003;92:1287–93. **6.** Pijlman AH, et al. Atherosclerosis. 2010;209:189–94. **7.** Arca M, et al. Diabetes Metab Syndr Obes. 2011;4:155–66. **8.** Betteridge DJ, et al. Nat Rev Endocrinol. 2013;doi:10.1038/nrendo.2012.254. **9.** Avorn J, et al. JAMA. 1998;279(18):1458–62. **10.** Casula M, et al .Patient Preference and Adherence 2012;6:805–14. **11.** Stein E, et al. Am Heart J. 2004;148: 447–55.

Thank You!