Establish the Standard of Care for Dyslipidemia on High Risk Patients

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Presenter disclosure

- I hereby disclose that my relationship with Merck Sharp & Dohme (I.A.) Corp. Taiwan Branch includes:

  Speaker

Outline

- Importance of lipid control in high risk patients
- Updated lipid management guideline
- Current lipid control status in Taiwan
- Clinical data of combination of statin & ezetimibe
- Conclusions

Outline

Importance of lipid control in high risk patients

Updated lipid management guideline

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Conclusions

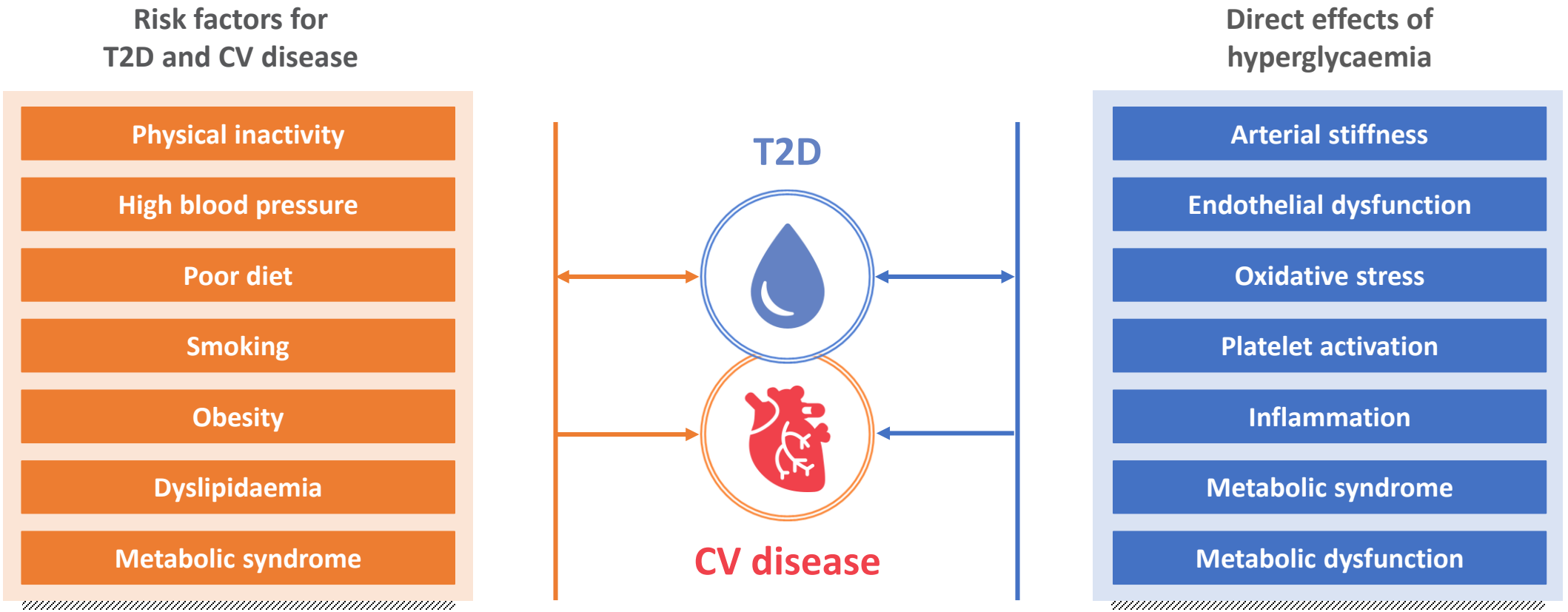
Who are High Risk Patients ?

- Atherosclerotic cardiovascular diseases (ASCVD)
  - Coronary artery disease (CAD)
  - Ischemic stroke
  - Peripheral arterial disease (PAD)
- Diabetes mellitus (DM)
- Chronic kidney disease (CKD)
- Familial hypercholesterolemia (FH)

J Formos Med Assoc. 2017 Apr;116(4):217-248.

Pathophysiology of CV disease in patients with T2DM is complex

T2D shares common risk factors with CV disease and contributes to vascular damage

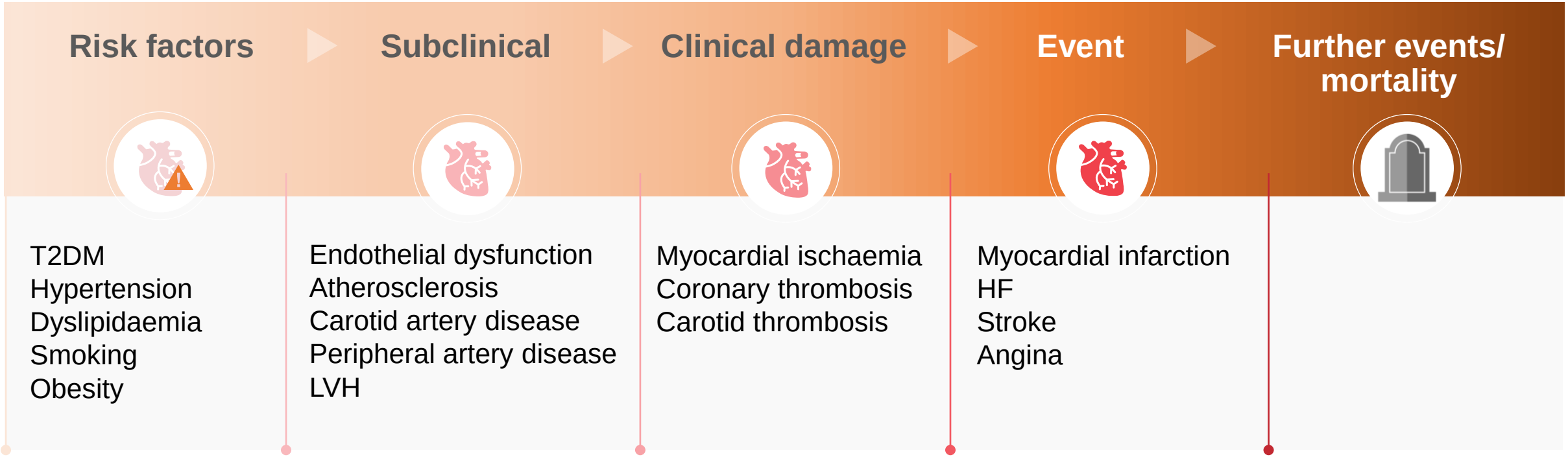


CV, cardiovascular; T2D, type 2 diabetes

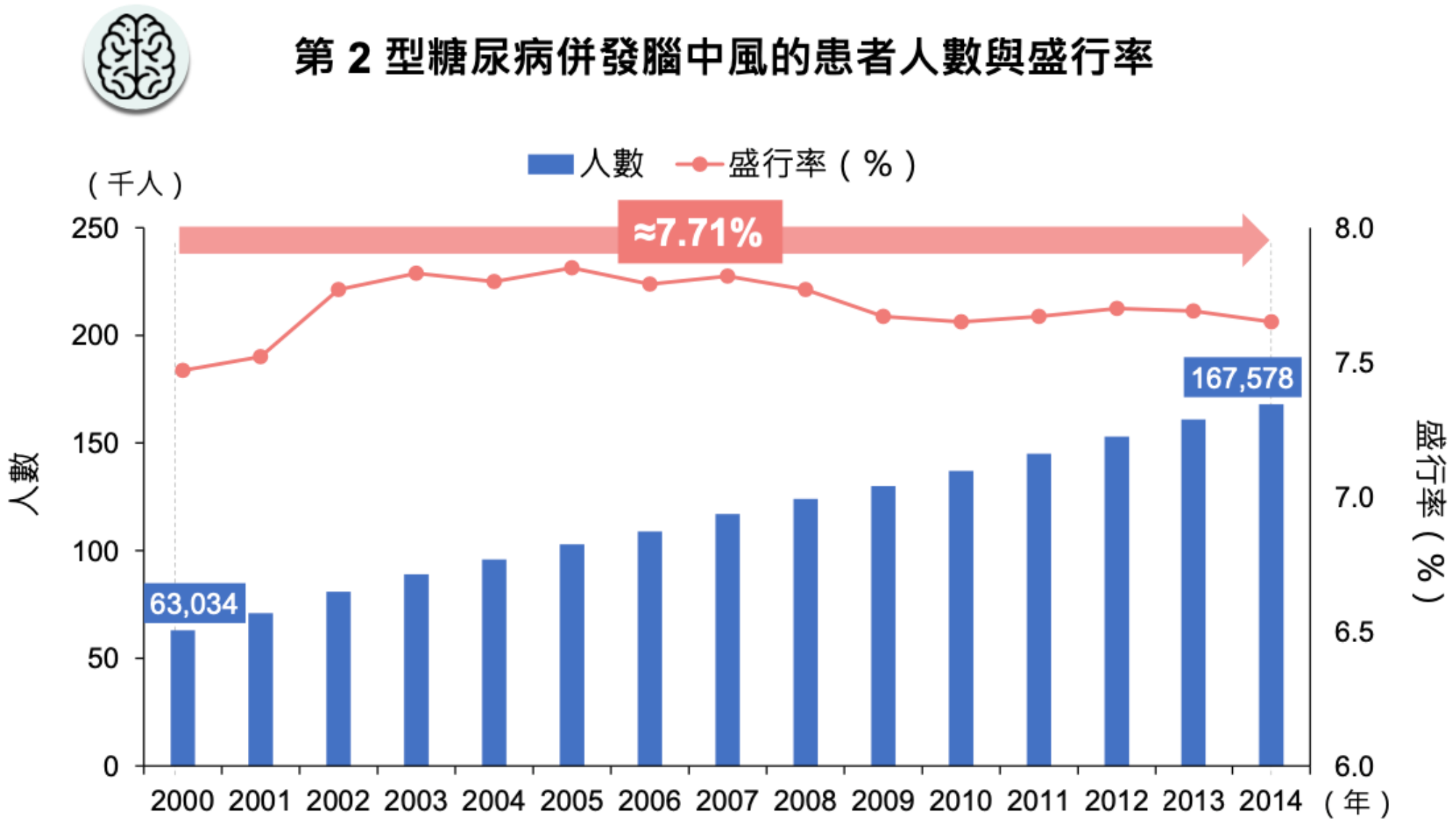
Newman JD *et al. J Am Coll Cardiol* 2017;70:883

Cardiovascular disease exists as a continuum

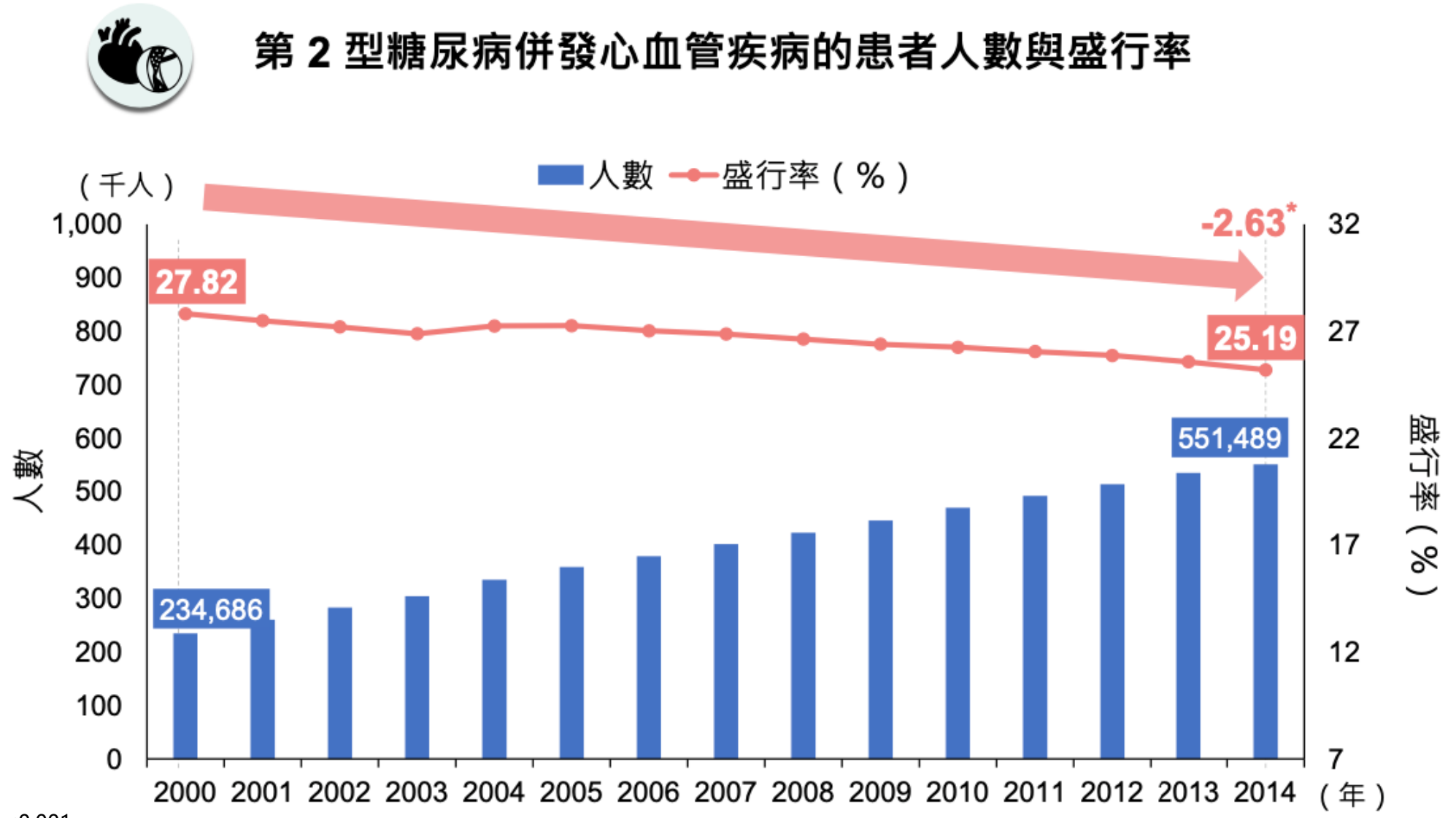
- Patients are at CV risk throughout the pathophysiological course, even before diagnosis



台灣 T2DM 併發腦中風的盛行率持平



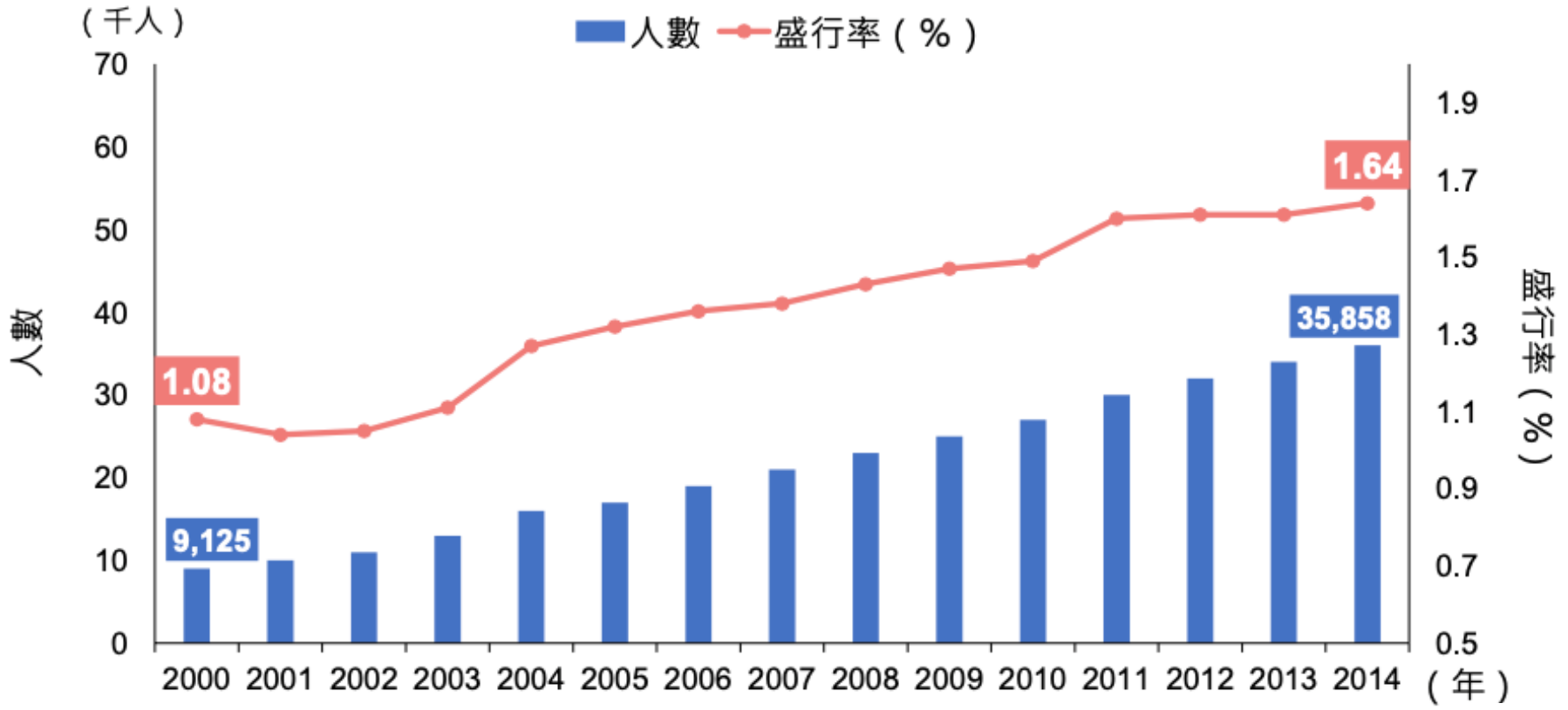
台灣 T2DM 併發心血管疾病的盛行率逐年下降



*盛行率下降趨勢 p<0.001

台灣 T2DM 併發周邊血管疾病的盛行率逐年上升

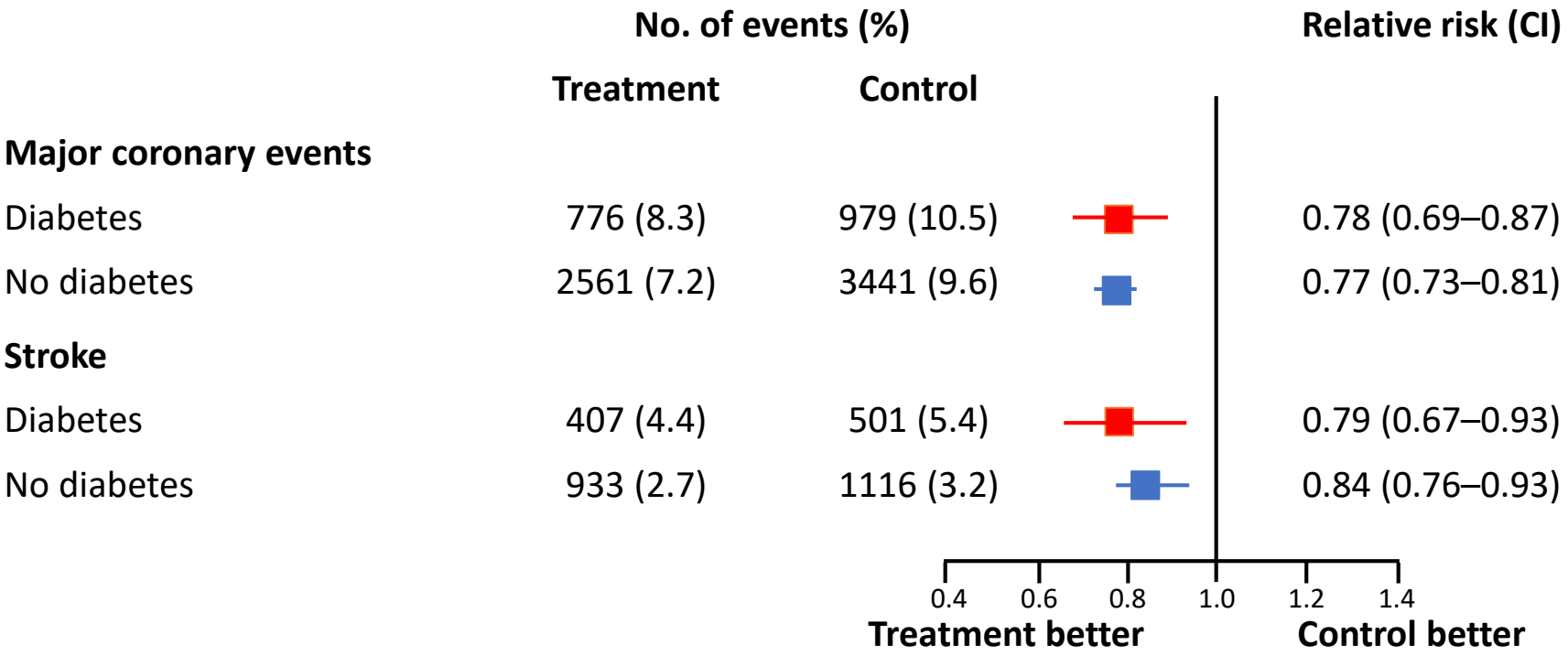
第 2 型糖尿病併發週邊血管疾病的患者人數與盛行率



盛行率上升趨勢 $p < 0.001$

Cholesterol Treatment Trialists meta-analysis: Major CV events in diabetes and non-diabetes

(N=18,686)



Proportional effects per 1 mmol/L (40 mg/dL) reduction in LDL-C

- CI=confidence interval; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol

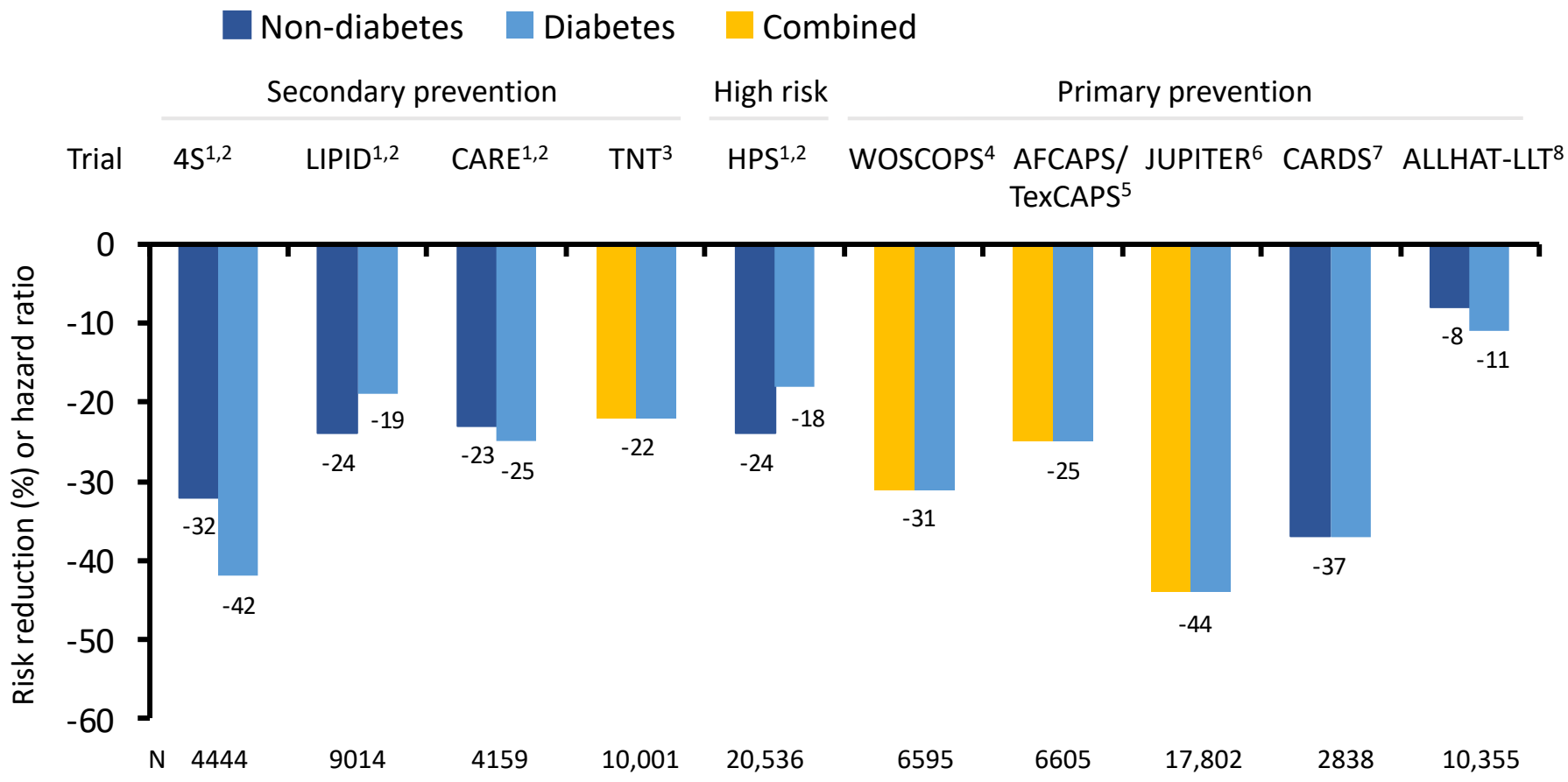
Cholesterol Treatment Trialists Collaborators. Lancet 2008;371:117-125

Reduction in 10-year risk of major CVD in major statin trials in diabetic subjects (n=16,032)

Study (ref.)	CVD	Statin dose and comparator	Risk reduction (%)	Relative risk reduction (%)	Absolute risk reduction (%)	LDL cholesterol reduction (mg/dl)	LDL cholesterol reduction (%)
4S-DM (215)	2°	Simvastatin 20–40 mg vs. placebo	85.7 to 43.2	50	42.5	186 to 119	36
ASPEN 2° (220)	2°	Atorvastatin 10 mg vs. placebo	39.5 to 24.5	34	15	112 to 79	29
HPS-DM (216)	2°	Simvastatin 40 mg vs. placebo	43.8 to 36.3	17	7.5	123 to 84	31
CARE-DM (217)	2°	Pravastatin 40 mg vs. placebo	40.8 to 35.4	13	5.4	136 to 99	27
TNT-DM (218)	2°	Atorvastatin 80 mg vs. 10 mg	26.3 to 21.6	18	4.7	99 to 77	22
HPS-DM (216)	1°	Simvastatin 40 mg vs. placebo	17.5 to 11.5	34	6.0	124 to 86	31
CARDS (221)	1°	Atorvastatin 10 mg vs. placebo	11.5 to 7.5	35	4	118 to 71	40
ASPEN 1° (220)	1°	Atorvastatin 10 mg vs. placebo	9.8 to 7.9	19	1.9	114 to 80	30
ASCOT-DM (219)	1°	Atorvastatin 10 mg vs. placebo	11.1 to 10.2	8	0.9	125 to 82	34

Diabetes Care, Vol 34, Suppl 1, S29-31, 2011

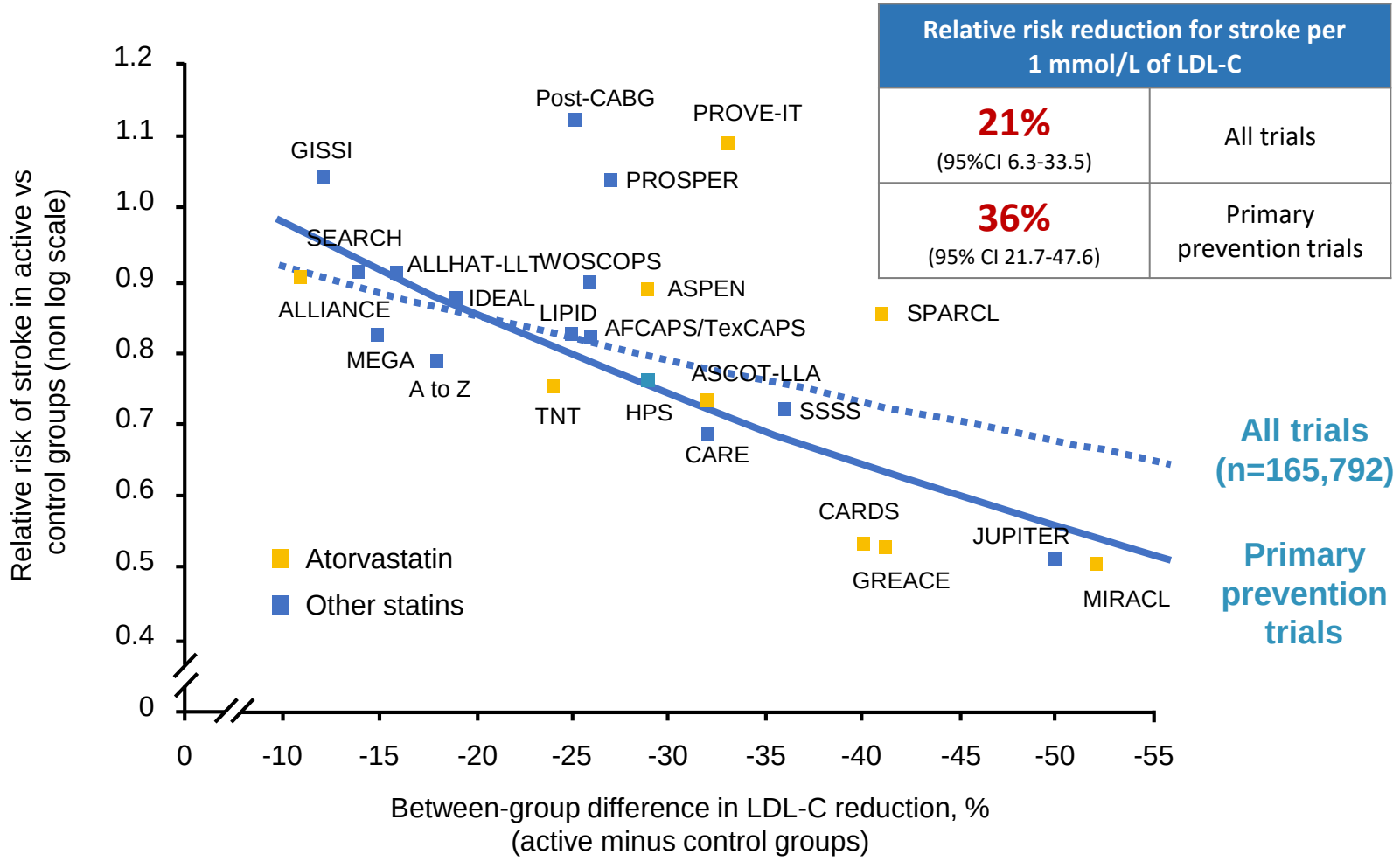
Statin therapy and CVD prevention



1. Ryden L et al. Eur Heart J 2007;28:88-136;
2. Libby P. J Am Coll Cardiol 2005;46:1225-1228;
3. LaRosa J et al. N Engl J Med 2005;352:1425-1435;
4. Shepherd J et al. N Engl J Med 1995;333:1301-1307;
5. Downs J et al. JAMA 1998;279:1615-1622;
6. Ridker P et al. N Engl J Med 2008;359:2195-2207;
7. Colhoun H et al. Lancet 2004;364:685-696;
8. ALLHAT-LLT. JAMA 2002;288:2998-3007

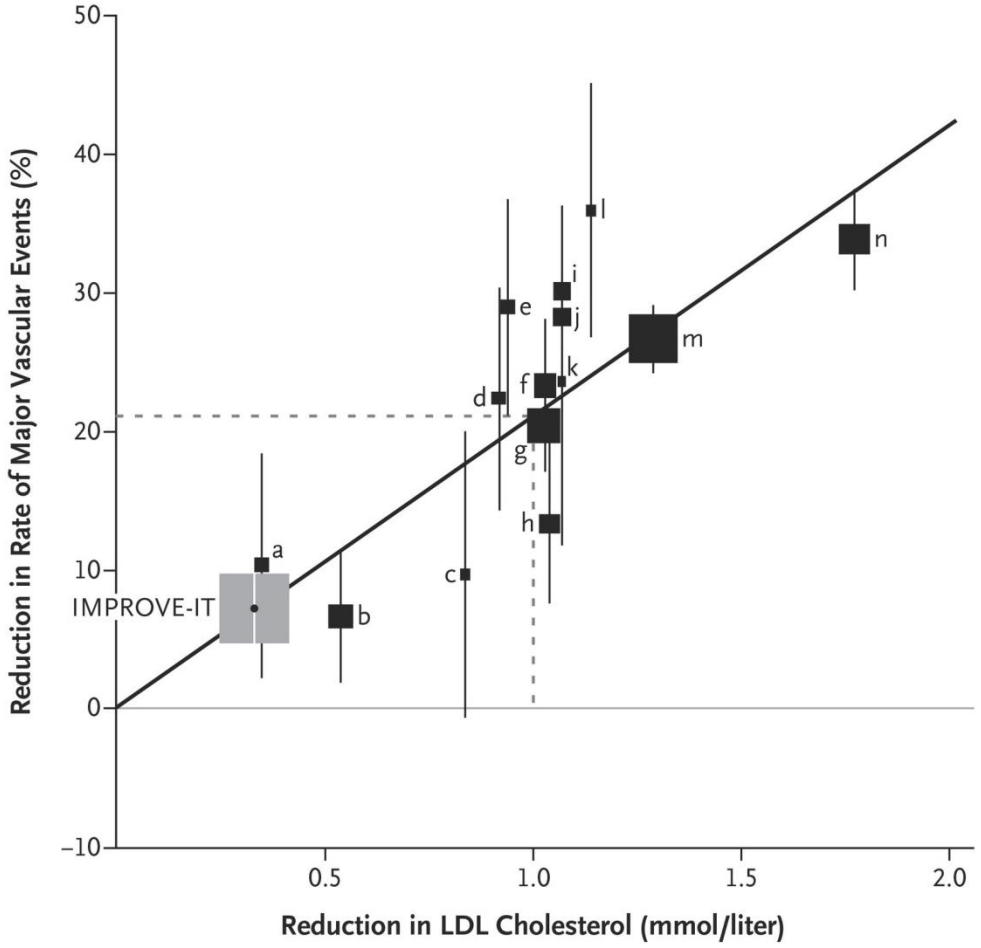
- CVD=cardiovascular disease

Each 39 mg/dL (1.0 mmol/L) reduction in LDL-C reduced stroke by 36% in primary prevention trials



Amarenco P et al. . Lancet Neurol 2009;8:453–463

Modelling the impact of LDL lowering
Relative risk reduction is related to absolute LDL decrease



Data from trials of:

- Statin vs. placebo
- More vs. less intense statin therapy
- Combination therapy with ezetimibe
- Combination therapy with PCSK9i

Regression line reveals:

1.0 mmol/l fall in LDL-C translates into a 22% decrease in CV risk

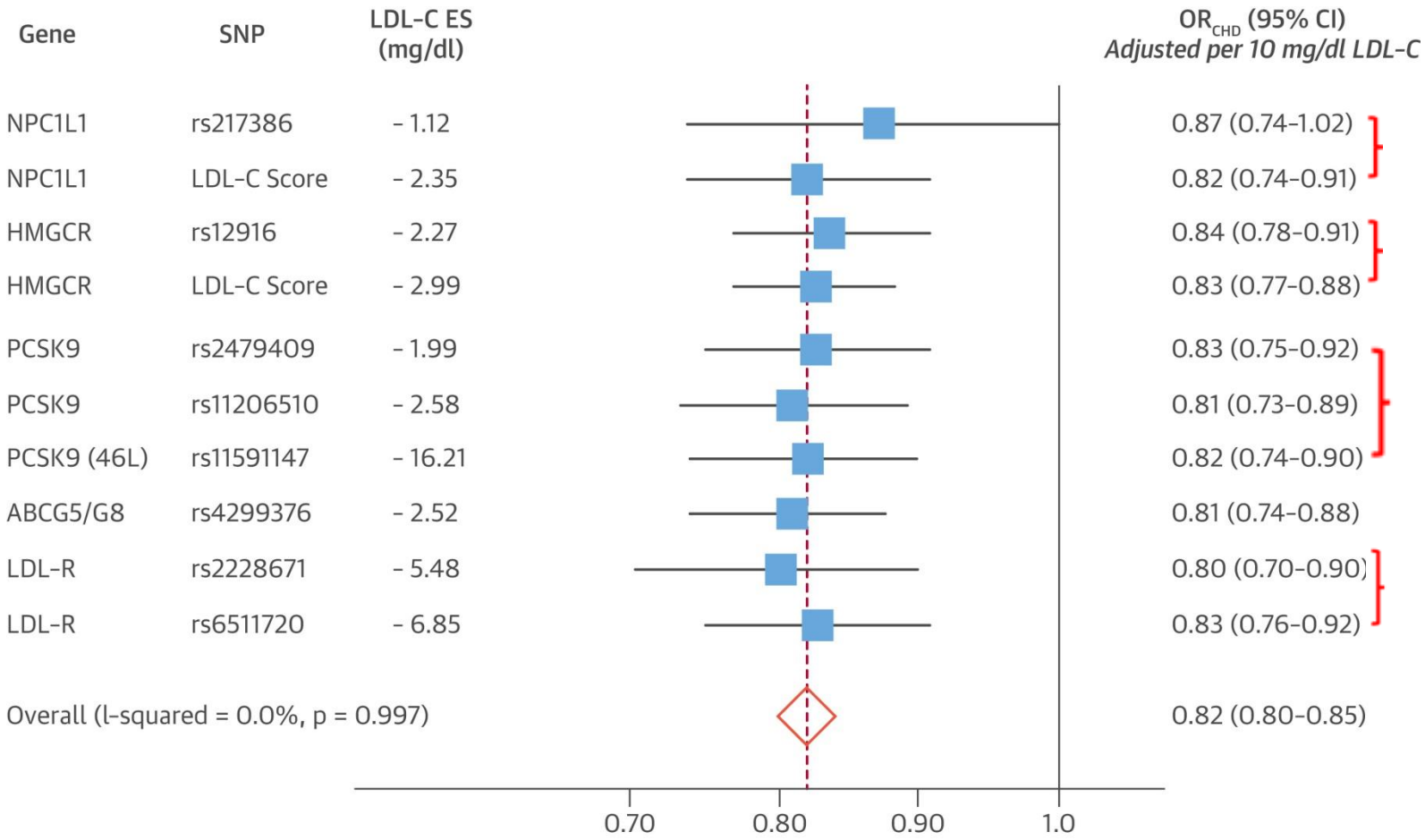
LDL-C: 1 mmol/l = 38.67 mg/dL

CTTC. Lancet 2005; 366: 1267-78
Cannon CP, et al. N Engl J Med 2015; 372: 2387-97

LDL-C lowering – the common final pathway to CHD risk reduction

*10 mg/L LDL-C → 18% Lower Risk for CHD***

i.e. 1 mmol/l (38.67 mg/dL) lower LDL-C → ~70% Lower risk for CHD



LDL lowering due to inherited variation in :

Cholesterol absorption

Cholesterol production

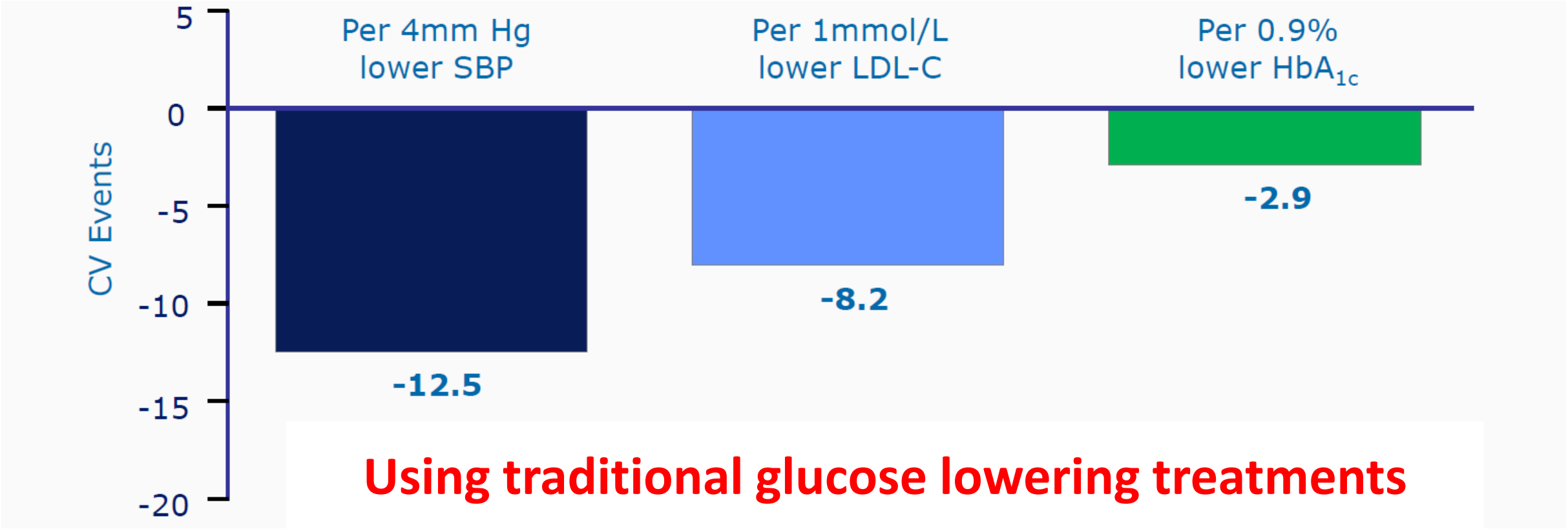
LDL receptor number

Protective SNPs at ATP-binding cassette (ABC) transporters/ LDL receptor loci

CHD risk reduction per unit LDL decrease is independent of underlying mechanism

Ference BA. Et al. J Am Coll Cardiol 2015; 65: 1552-61

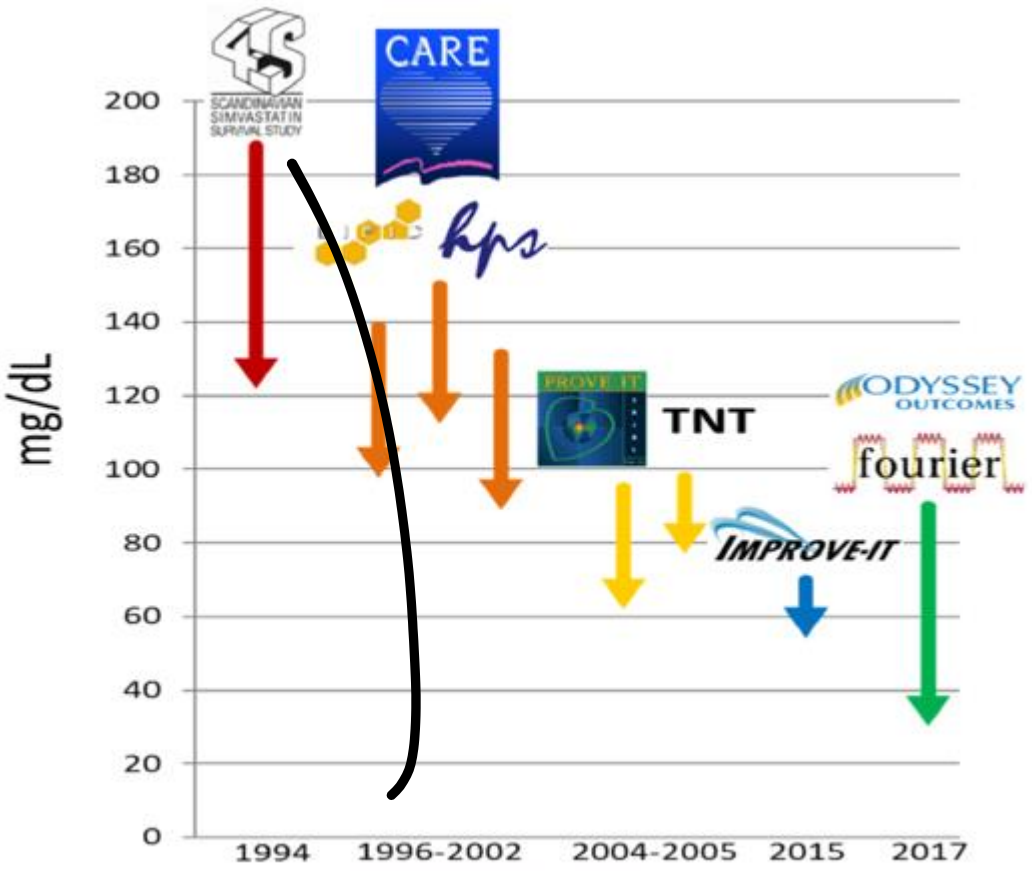
Benefit of different interventions per 200 patients with diabetes treated for 5 years



Using traditional glucose lowering treatments

Ray, *Lancet 2009* Meta-analysis of intensive glucose-lowering trials.

A Quarter of a Century of Treating LDL-Cholesterol



An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Even lower LDL-C levels beyond LDL-C reduction target give additional CV benefit

High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

Courtesy of M. Sabatine and R. Giugliano

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ADA guideline on lipid management in patients with diabetes

2018

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

2019

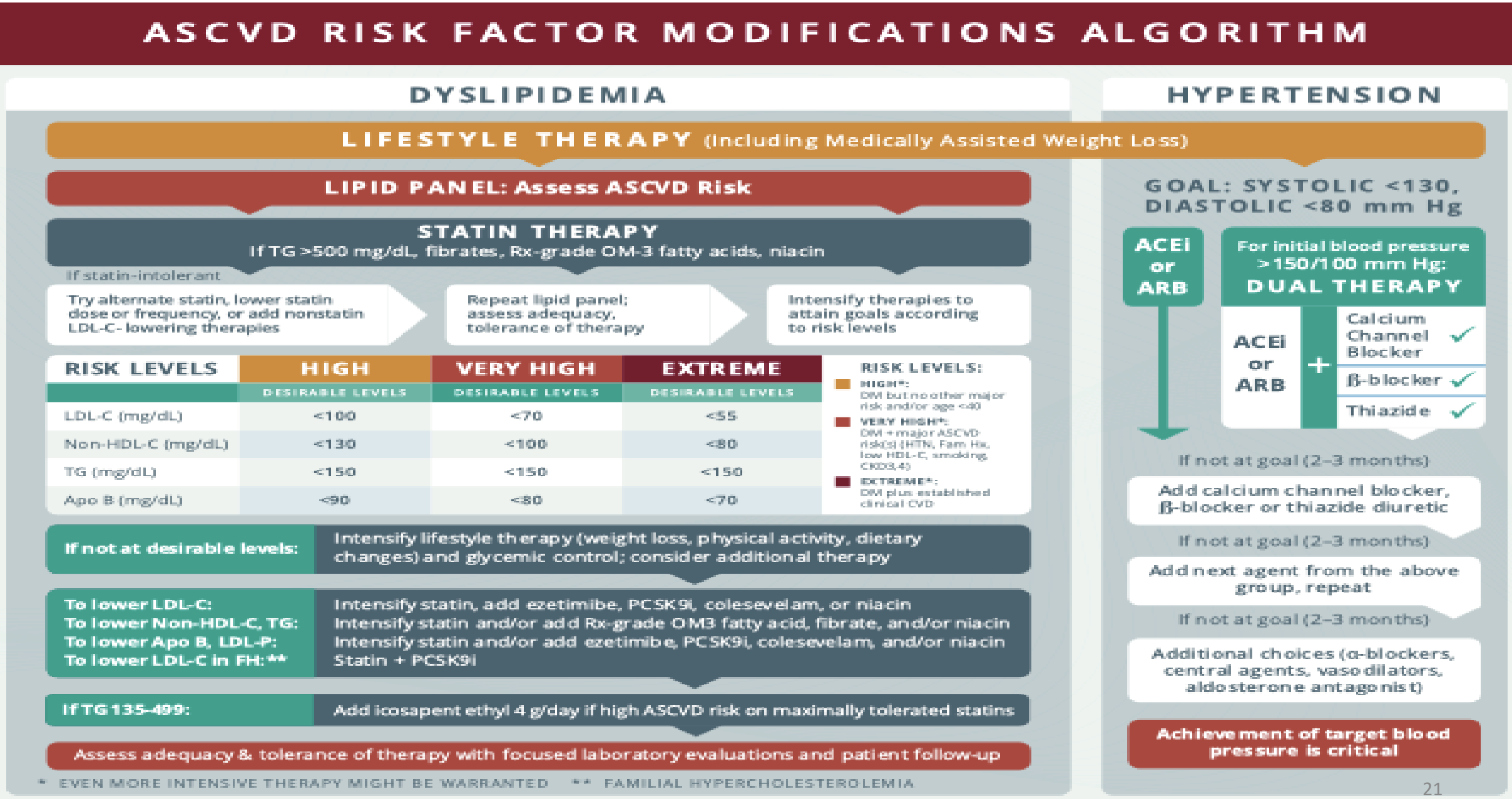
Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ACSVD risk factors :
LDL-C ≥100 mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

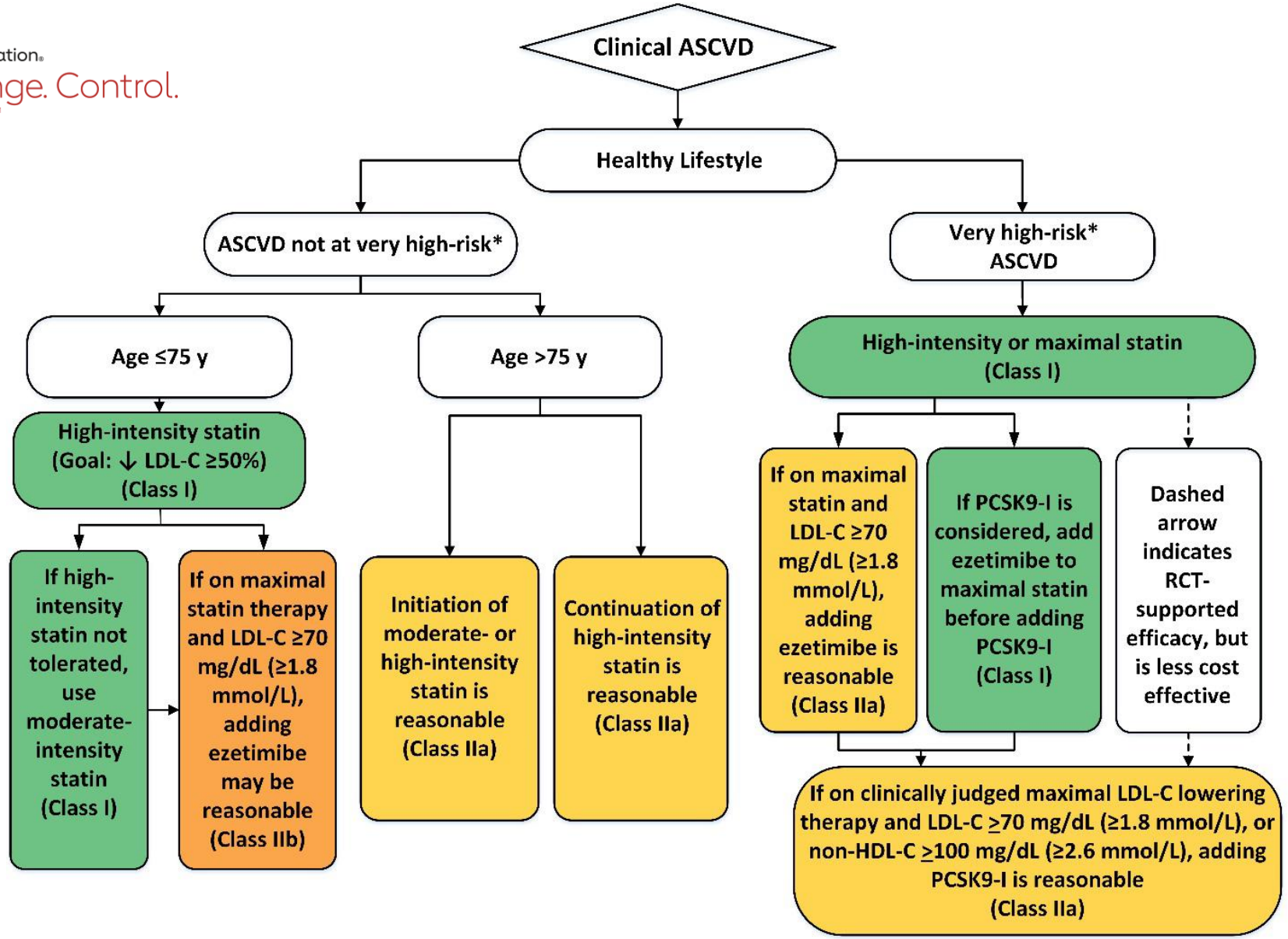
ADA : American Diabetes Association

2020 AACE/ACE Consensus Statement



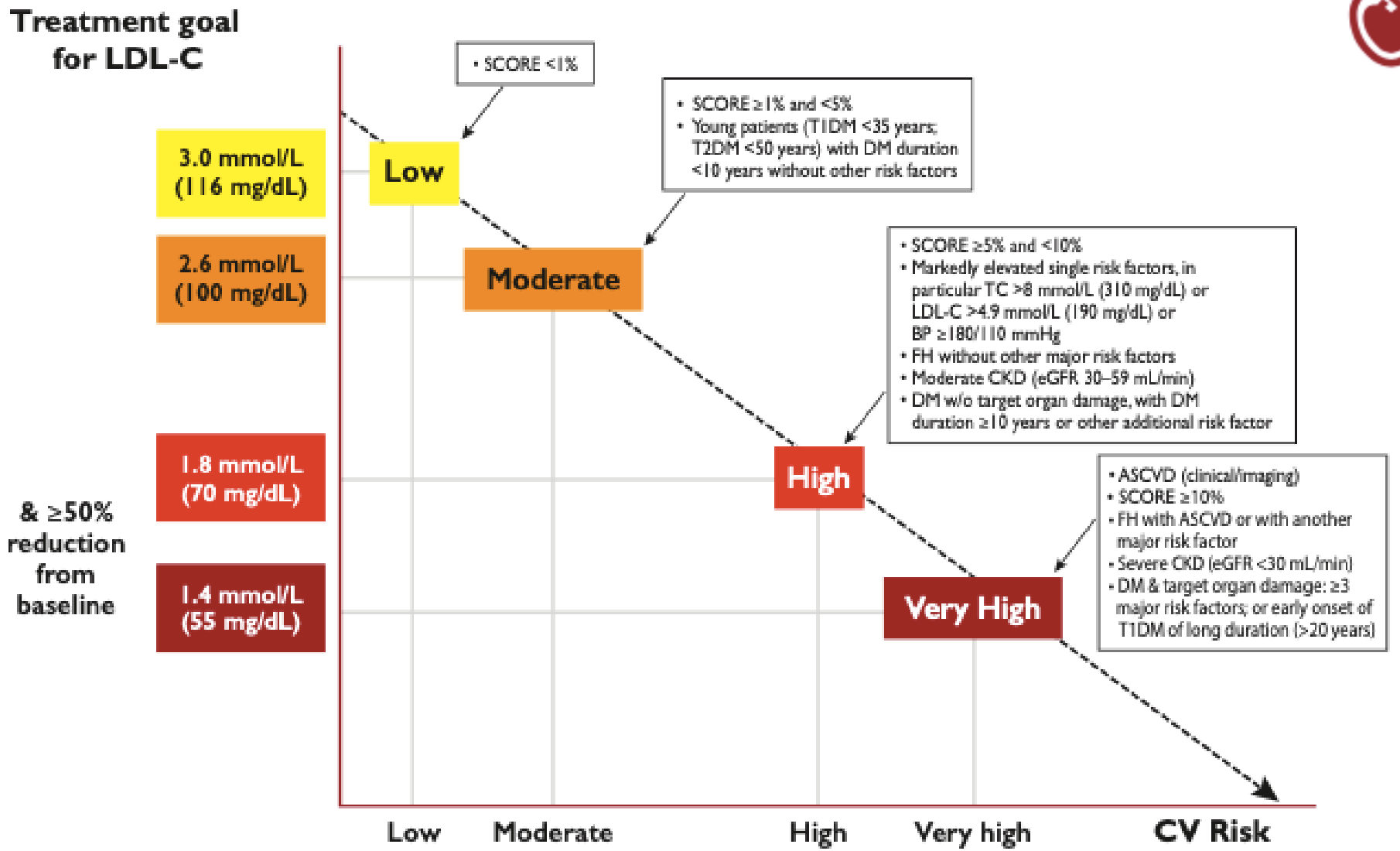
2018 AHA Guideline on the management of blood cholesterol

American Heart Association.
Check. Change. Control. Cholesterol™



Circulation. 2018 Nov 10

Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular disease risk



European Heart Journal (2019) 00, 1~78

LDL-C Treatment for high risk patients

ESC European Society of Cardiology

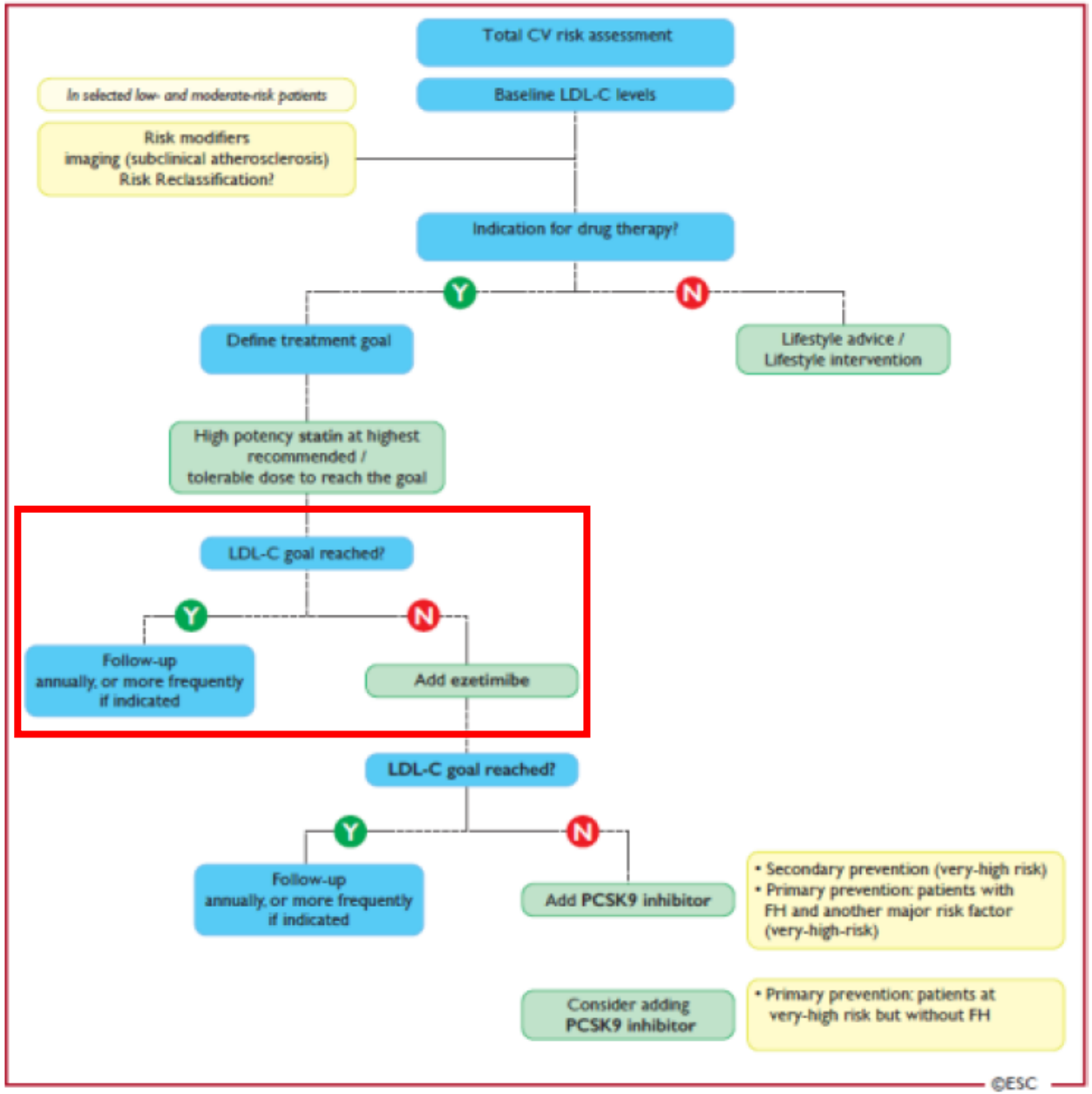
In DM patients

- **Very high risk: LDL-C goal <55mg/dL**
  - Patients with DM + 1 of the following:
    - With established CVD
    - Other target organ damage
    - 3 or more major risk factors
    - Early onset T1DM of long duration
- **High risk: LDL-C goal <70mg/dL**
  - Patients with DM duration >10 years
    - Without target organ damage
    - And without any other additional risk factors
- **Moderate risk: LDL-C goal <100mg/dL**
  - Young patients (T1DM aged <35 or T2DM aged <50)
    - With DM duration <10 years
    - And without other risk factors

In CKD patients

- **Very High Risk: LDL-C goal <55mg/dL**
  - Stage 3-5 CKD: eGFR <30 mL/min/1.73 m^2
- **High Risk: LDL-C goal: <70mg/dL**
  - eGFR 30-59 mL/min/ 1.73 m^2

European Heart Journal (2019) 00, 1~78



EAS ESC
European Society of Cardiology

Treatment algorithm for pharmacological LDL-C lowering

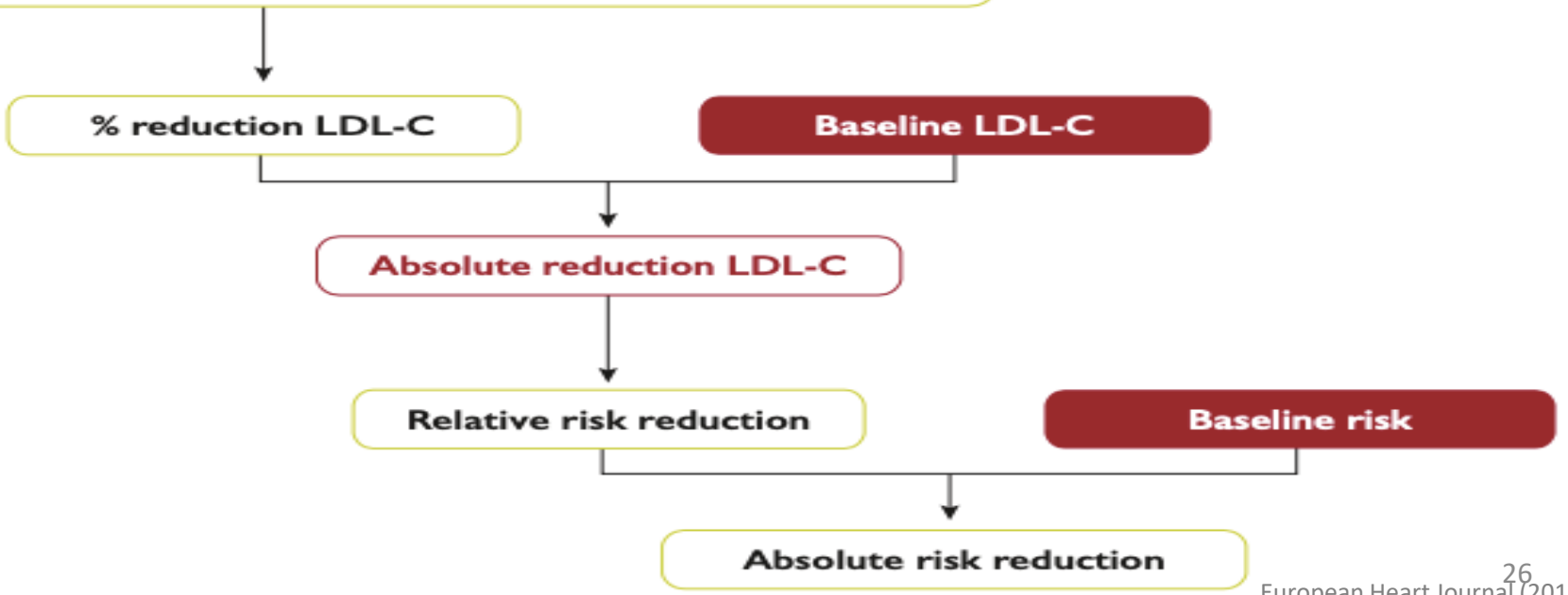
- Maximal statin dose
- **4-6 weeks** LDL-C not at goal + ezetimibe
- **4-6 weeks** LDL-C not at goal + PCSK9i

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Expected clinical benefits of LDL-C lowering therapies

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%



European Heart Journal (2019) 00, 1~78

血脂異常

臨床建議	證據等級	臨床建議強度	華人資料
糖尿病人建議**每年至少接受1次**血脂的檢查，包括 :總膽固醇、低密度脂蛋白膽固醇、高密度脂蛋白膽固醇和三酸甘油酯。	中	中等建議	
沒有心血管疾病的糖尿病人，低密度脂蛋白膽固醇的治療**目標是低於 100mg/dL** 或是降低 30-40%。	高	強烈建議	
罹患心血管疾病的糖尿病人，低密度脂蛋白膽固醇的治療**目標是低於 70mg/dL** 或是降低 30-40%。	中	中等建議	
三酸甘油酯的治療目標最好能低於 150mg/dL，高密度脂蛋白膽固醇的治療目標最好能 : 男性高於40mg/dL 、女性高於50mg/dL。	低	中等建議	

血脂異常

臨床建議	證據等級	臨床建議強度	華人資料
如果沒有禁忌症，建議糖尿病人使用 Statins 類藥物來降低低密度脂蛋白膽固醇。	中	強烈建議	
懷孕是 statins 類藥物的絕對禁忌症。	低	建議不使用	
Statins 類藥物，若病人無法承受高劑量或使用高劑量但無法達標 建議合併 ezetimibe 以達 LDL治療目標。	中	強烈建議	

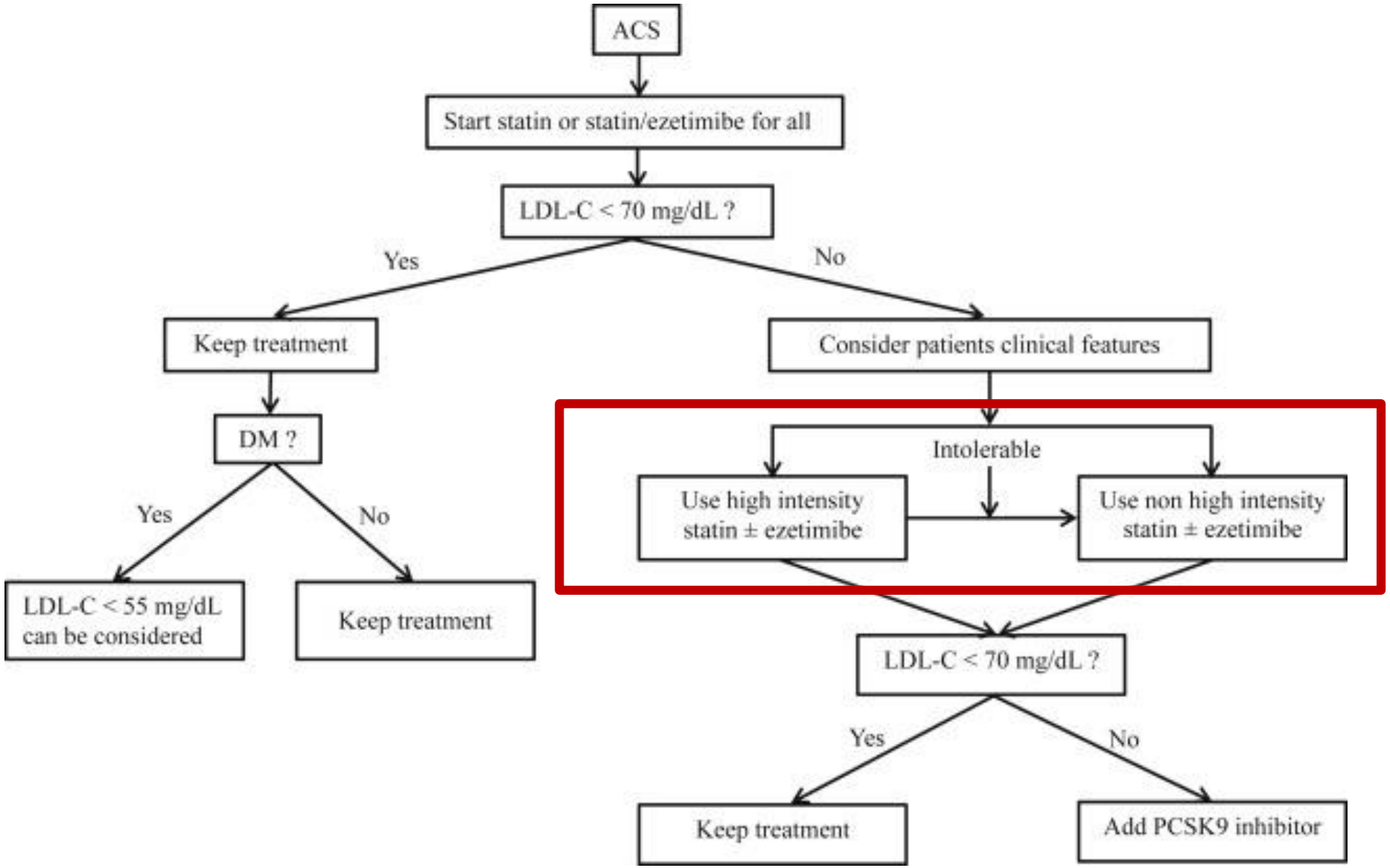
生活型態的介入治療對所有血脂異常的糖尿病人均需要。包括規律運動、戒菸、減重及飲食的改善。

2017 Taiwan Lipid Guidelines for High-risk Patients
LDL-C Treatment Target

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 Apr;116(4):217-248

2017 Taiwan Lipid Guidelines for High-risk Patients



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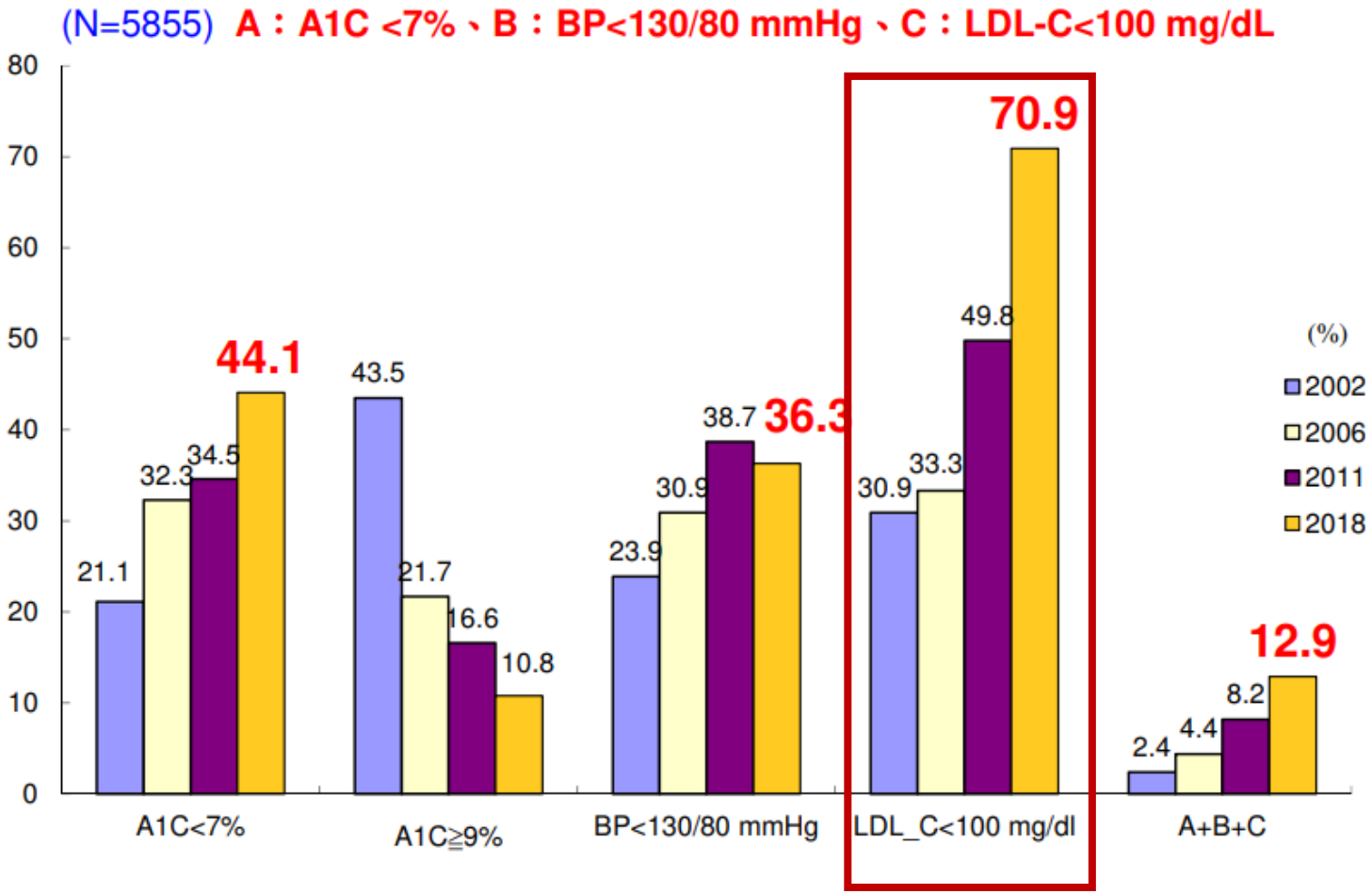
台灣糖尿病健康促進機構之品管調查研究

三高控制狀況- TADE 2002/2006/2011/2018 調查



https://www.tade.org.tw/upload/News/file/1529-1.pdf

台灣糖尿病健康促進機構之品管調查研究

品管調查－資料分析（基本資料一）

項目 (N=5855)	所有對象 (Mean ± SD)	男性 (Mean ± SD)	女性 (Mean ± SD)
年齡 (yr)	62.3± 12.1	61.3± 12.2	63.3±11.9
病程 (yr)	11.2± 8.5	11.0± 8.3	11.3± 8.8
BMI (kg/m^2)	26.3± 4.4	26.3± 4.2	26.2± 4.6
腰圍 (cm)	90.6± 11.1	93.2± 10.6	88± 11.1
收縮壓 (mmHg)	132± 16.9	132.2± 16.1	133.2± 17.5
舒張壓 (mmHg)	75.4± 11.5	76.6± 11.2	74.2± 11.8
餐前血糖 (mg/dL)	139.7± 45.6	139.1± 43.8	140.3± 47.4
A1C (%)	7.4± 1.3	7.4± 1.4	7.4± 1.3
Ser-Cr (mg/dL)	1.4± 7.2	1.7± 9.0	1.2± 4.9
TC (mg/dL)	159.7± 50.0	155.5± 37.8	164± 59.6
TG (mg/dL)	139.5±106.1	142.1±111.5	136.9±100.4
LDL-C (mg/dL)	88.4± 27.0	87.6± 27.0	89.2± 27.1
HDL-C (mg/dL)	48.5± 17.9	45.7± 18.4	51.4± 16.8

https://www.tade.org.tw/upload/News/file/1529-1.pdf

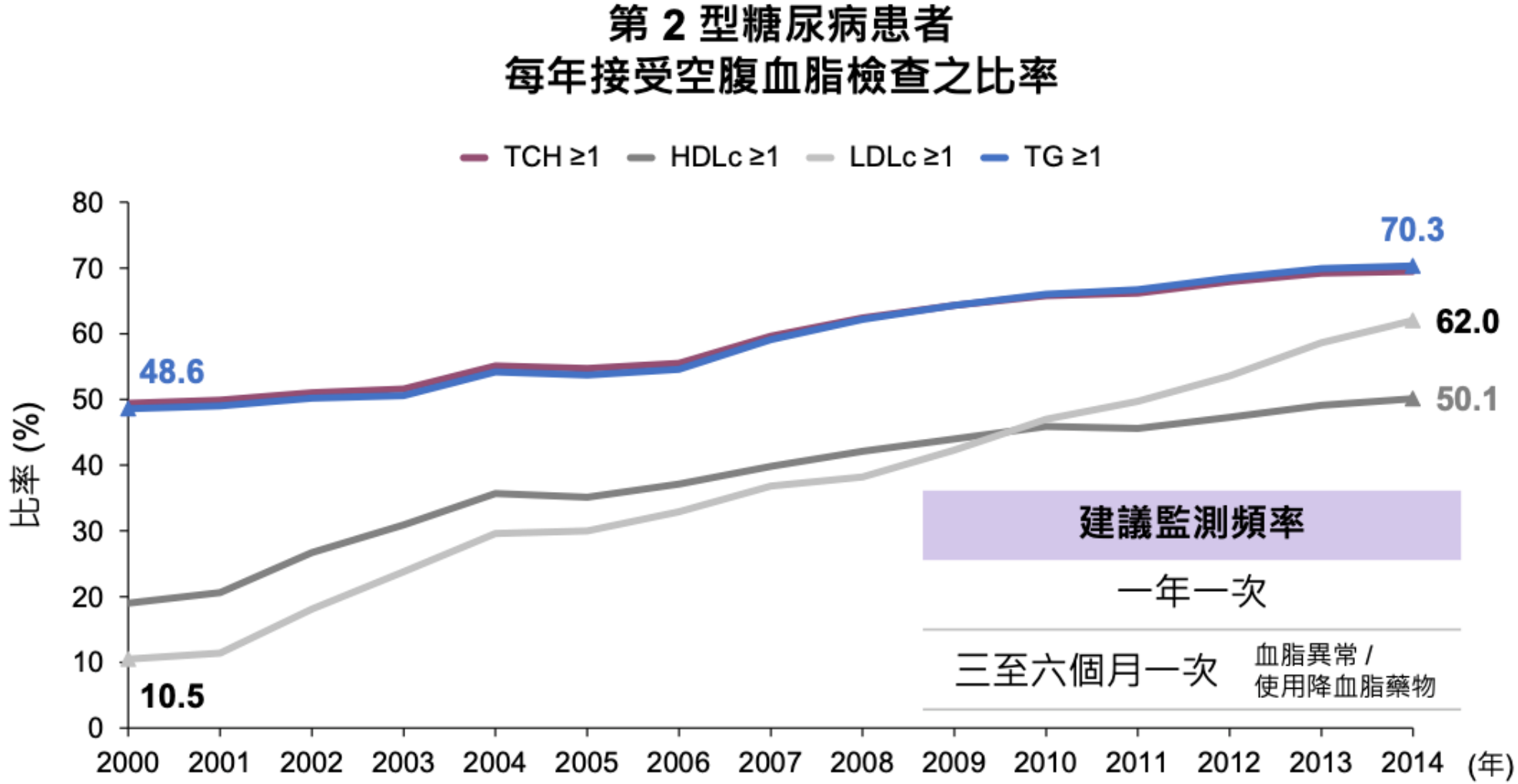
台灣糖尿病健康促進機構之品管調查研究

品管調查－資料分析（基本資料二）

項目(N=5855)	所有對象(%)	男性(%)	女性(%)
有參與共照網計畫	92.1	92.6	91.6
抽菸	26.6	48.0	4.6
類型　第1型(T1DM)	2.0	1.7	2.2
第2型(T2DM)	98.0	98.3	97.7
藥物治療			
近半年有使用慢箋	95.6	95.6	95.6
有使用抗血小板製劑	17.6	21.0	14.1
有高血壓藥物治療	55.1	54.3	55.9
有高血脂藥物治療	71.5	70.0	73.1
有口服糖尿病藥物	91.6	91.3	91.9
有注射糖尿病藥物	29.3	29.7	28.8

https://www.tade.org.tw/upload/News/file/1529-1.pdf

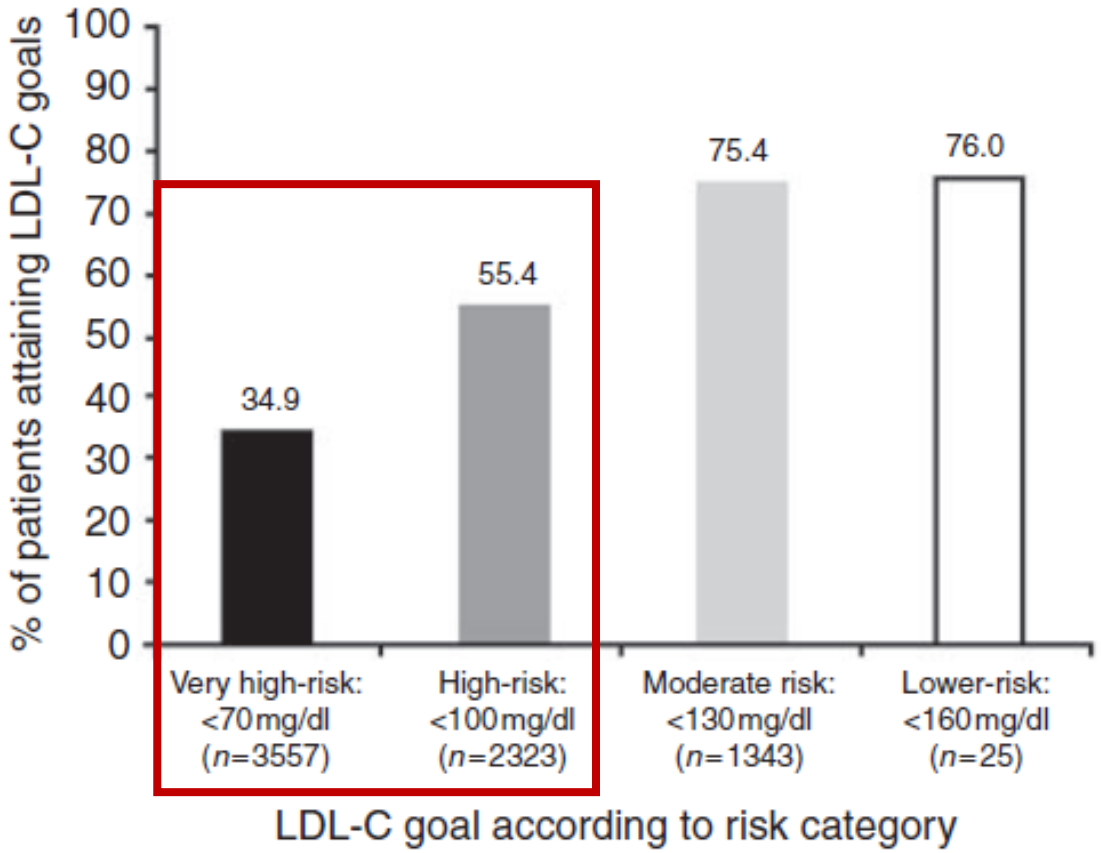
空腹血脂檢查率逐年增加， 但有 30% 的患者未接受檢查



註: 1. 接受檢查比率= [(當年)接受檢查人數/(當年)糖尿病盛行數] x 100%
2. Total cholesterol (TCH) 09001; High-density lipoprotein cholesterol (HDLc) 09043 ;
Low-density lipoprotein cholesterol (LDLc) 09044 ; Triglyceride (TG) 09004。
TCH, total cholesterol 總膽固醇;HDLc, high density lipoprotein 高密度脂蛋白;LDLc, low-density lipoprotein 低密度脂蛋白; TG, triglyceride 三酸甘油脂

CEPHEUS Pan-Asian survey : Large proportion of very high risk patients not at goal and remain at risk for cardiovascular disease

7281 patients, 34.9% very high risk patients (established CVD plus diabetes/multiple risk factors; or patients with ACS)



index period: April - December 2008

European Journal of Preventive Cardiology 2011, 19(4) 781–794

Received: 14 February 2019 | Revised: 10 August 2019 | Accepted: 19 August 2019
DOI: 10.1111/jep.13286

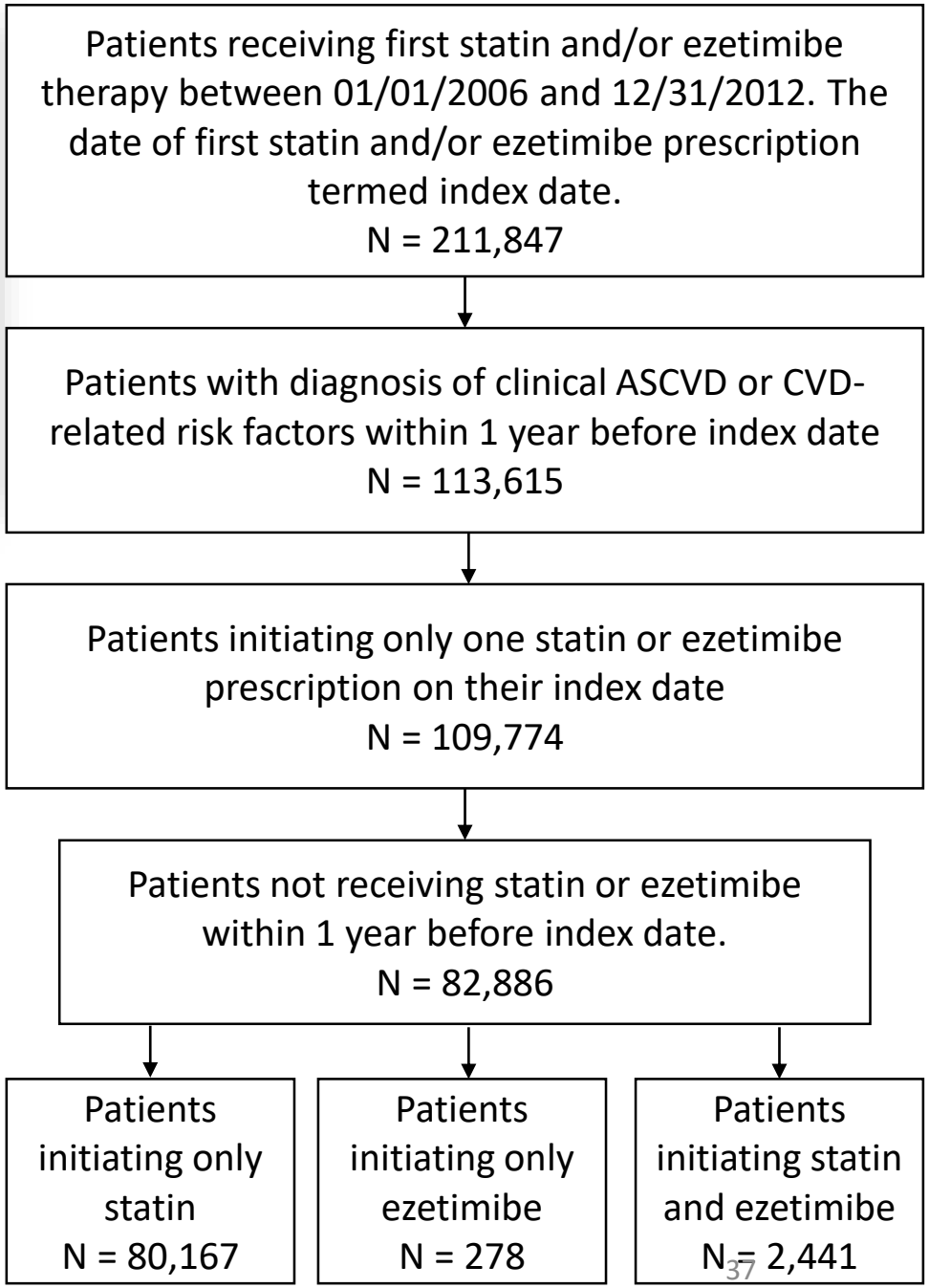
ORIGINAL PAPER

WILEY Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

Treatment patterns of lipid-lowering therapies and possible statin intolerance among statin users with clinical atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus (DM) in Taiwan

評估台灣ASCVD或DM患者使用「statin類藥物」或「statin合併ezetimibe」的治療模式以及「statin類藥物」可能引起的不耐受性

- A retrospective cohort study using Taiwan's 2005 to 2013 NHIRD.
- Patients with history of clinical ASCVD or DM (without previous clinical ASCVD) and initiating statin or statin plus ezetimibe therapy during 2006 to 2012
- 分析藥物的治療方式（包括停藥、重新使用、減藥、加藥、換藥）、藥物順從性（藥品持有率medication possession ratio, MPR)、用藥持續性（間隔小於60天），以及statin類藥物可能引起的不耐受性（從藥物使用開始追蹤12個月）



Chen WJ, et al. J Eval Clin Pract. 2019 Oct 23

高血脂症治療需要找出更有效率的方式

	Overall		By Index Lipid-lowering Agents				By History of Clinical ASCVD or CVD-related Risk Factors			
			Statin Only		Statin + Ezetimibe		Clinical ASCVD		Diabetes Mellitus but Without Clinical ASCVD	
Discontinuation										
Patients who discontinued treatment	49 265	59.64%	48 014	59.89%	1251	51.25%	5990	54.00%	17 869	57.46%
Patients with statin discontinuation only (n, column %[a])	48 017	97.47%	48 014	100.00%	3	0.24%	5806	96.93%	17 420	97.49%
Patients with statin and ezetimibe discontinuation (n, column %[a])	1234	2.50%	0	0.0%	1234	98.64%	181	3.02%	442	2.47%
Patients with ezetimibe discontinuation only (n, column %[a])	14	0.03%	0	0.0%	14	1.12%	3	0.05%	7	0.04%

1. 台灣的族群中有過半數(59.64%)的患者停止使用降血脂治療
2. 進一步分析可以發現，分別有54.0%的ASCVD患者(n=5,990)和57.5%的DM患者(n=17,869)停止使用藥物治療。

患者使用statin類藥物之平均藥物順從性(MPR)的整體表現也不佳(ASCVD患者 =0.62、DM患者 = 0.60)，

其中藥物順從性佳(MPR>0.8)的比例僅約三分之一(ASCVD患者=38.7% 、 DM 患者 = 33.4%) 。

用藥持續性也都未達半數，總體約為40%，其中ASCVD患者為 46.1% 、 DM患者為42.6%。

MPR : medication possession ratio

Chen WJ et al. J Eval Clin Pract 2019. Oct 23

高血脂症治療需要找出更有效率的方式

19.9%的ASCVD患者和21.4%的DM患者，可能對於statin類藥物產生不耐受性
(可能產生不耐受性的定義為劑量的改變、停藥、或是改用其他非statin類藥物)

	全部 (n=82,608)	次分析	
		ASCVD患者 (n=11,092)	DM患者 (n=31,100)
患者停止降血脂治療	59.64%	54.0%	57.5%
平均藥物順從性(MPR)	0.59	0.62	0.60
用藥持續性	40.43%	46.1%	42.6%
Statin類藥物可能的不耐受性	**22.10%**	**19.9%**	**21.4%**

Chen WJ et al. J Eval Clin Pract 2019. Oct 23

Outline

Importance of lipid control in high risk patients

Updated lipid management guideline

Current lipid control status in Taiwan

Clinical data of combination of statin & ezetimibe

Conclusions

Intensity of statin therapy

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

LDL-C = low density lipoprotein cholesterol

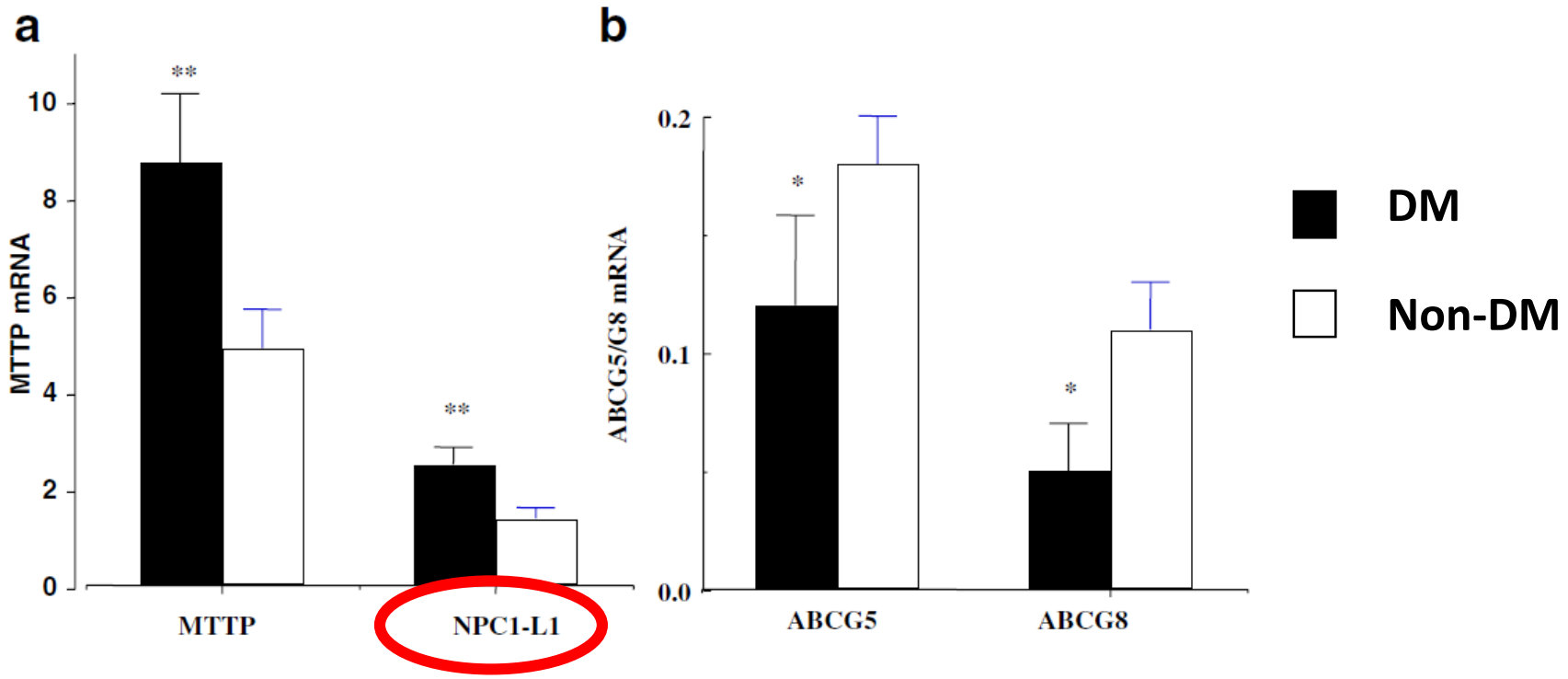
a The maximal dose approved for rosuvastain in Taiwan is 20 mg once daily. The 40 mg dose of rosuvastatin is reserved only for those patients who have familial hypercholesterolemia (FH).

J Formos Med Assoc. 2017 Apr;116(4):217-248.

S. Lally · C. Y. Tan · D. Owens · G. H. Tomkin

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

mRNA for NPC1L1 is up-regulated in diabetes



Diabetologia (2006) 49: 1008–1016

Ezetimibe: Mechanism of Action

- **Ezetimibe selectively inhibits intestinal cholesterol absorption**
  - ↓ intestinal delivery of cholesterol to the liver
  - ↑ expression of hepatic LDL receptors
  - ↓ cholesterol content of atherogenic particles
- **Ezetimibe and its active glucuronide metabolite circulate enterohepatically**
  - Delivers agent back to the site of action
  - Limits systemic exposure

Radiolabeled ezetimibe localized at brush border of small intestine

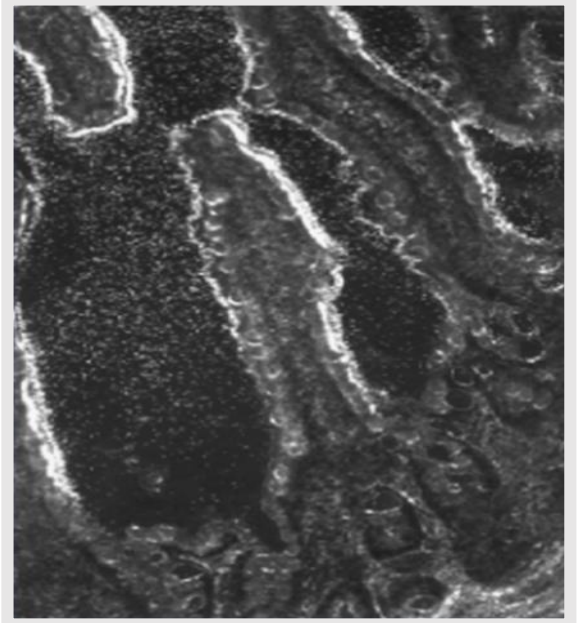
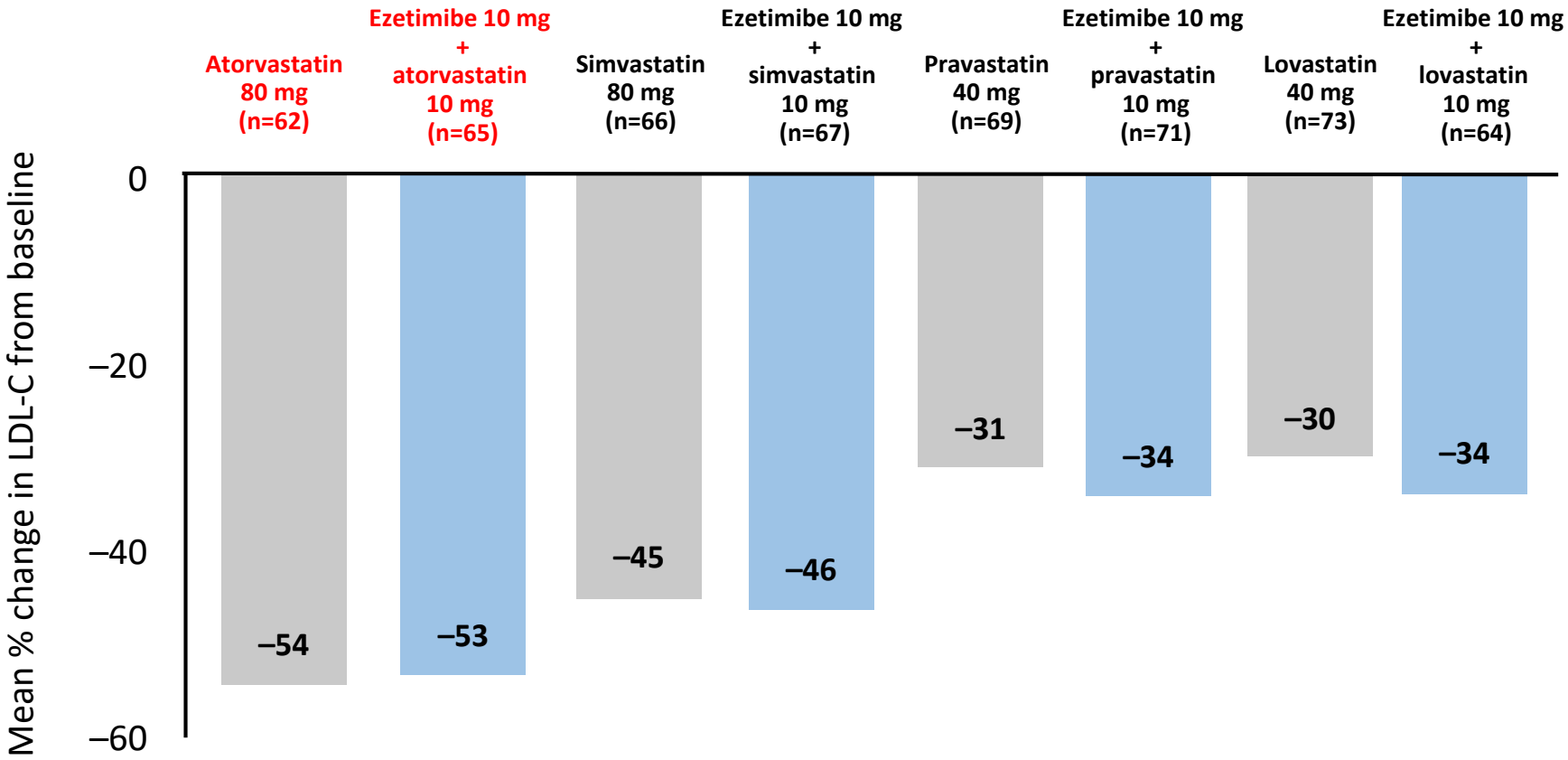


Photo courtesy of Harry R. Davis, PhD

Bays H. *Expert Opin Investig Drugs* 2002;11:1587-1604.
Catapano AL. *Eur Heart J Suppl* 2001;3:E6-E10.

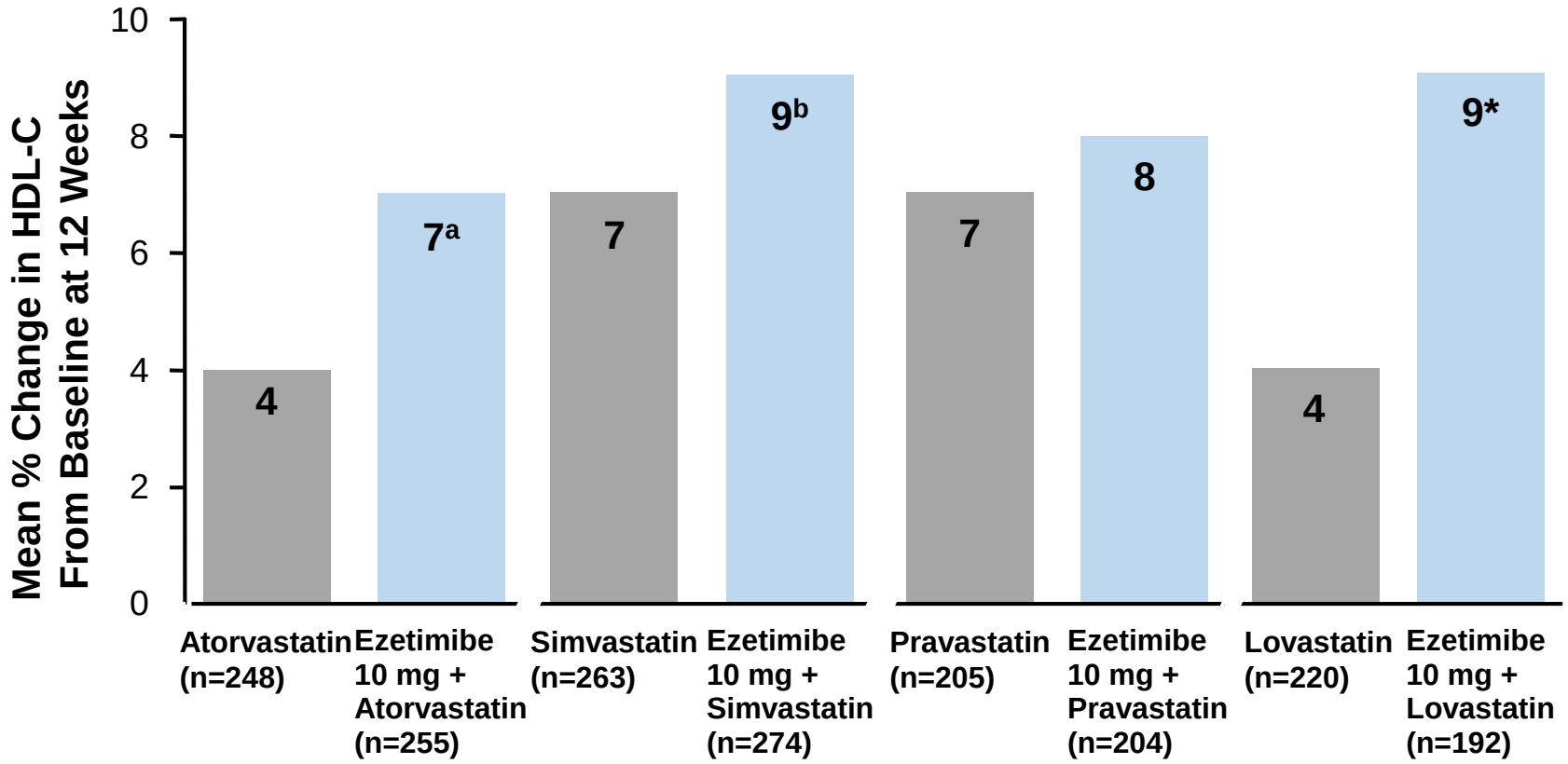
Ezetimibe + Statins versus High-Dose Statins

Ezetimibe 10 mg once daily together with the lowest statin dose reduced plasma LDL-C as much as or more than the highest dose tested of statin alone



- *Am J Cardiol* 2002;90:1084–1091

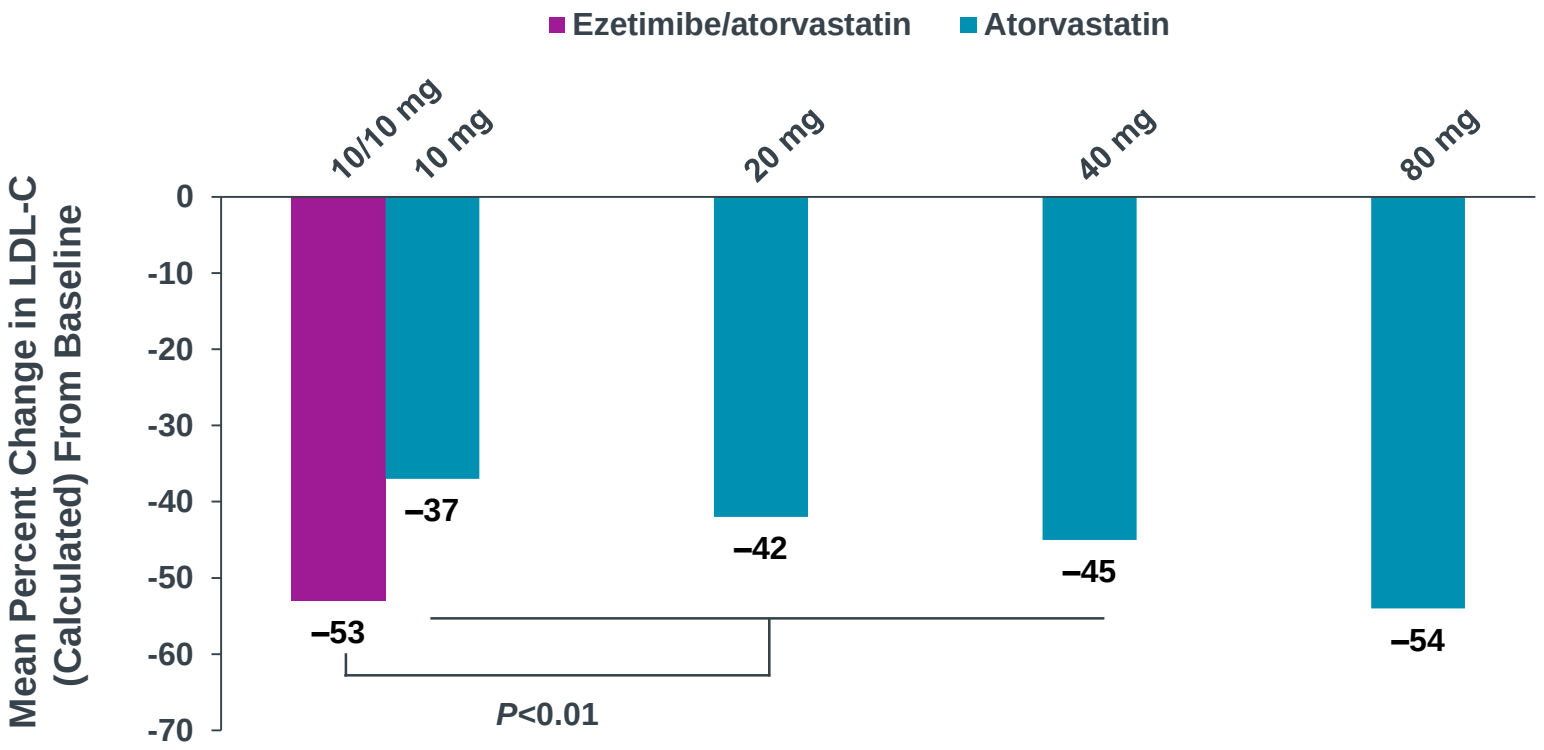
Ezetimibe Coadministered With Statins: Results for HDL-C



[a]*P*<0.01 ezetimibe + pooled statin doses versus pooled statin doses alone; [b]*P*=0.03 ezetimibe + pooled statin doses versus pooled statin doses alone

Ballantyne CM, et al. *Circulation*. 2003;107:2409–2415
Davidson MH, et al. *J Am Coll Cardiol.* 2002;40:2125–2134
Melani L, et al. *Eur Heart J.* 2003;24:717–728,1381
Kerzner B, et al. *Am J Cardiol.* 2003;91:418–424.

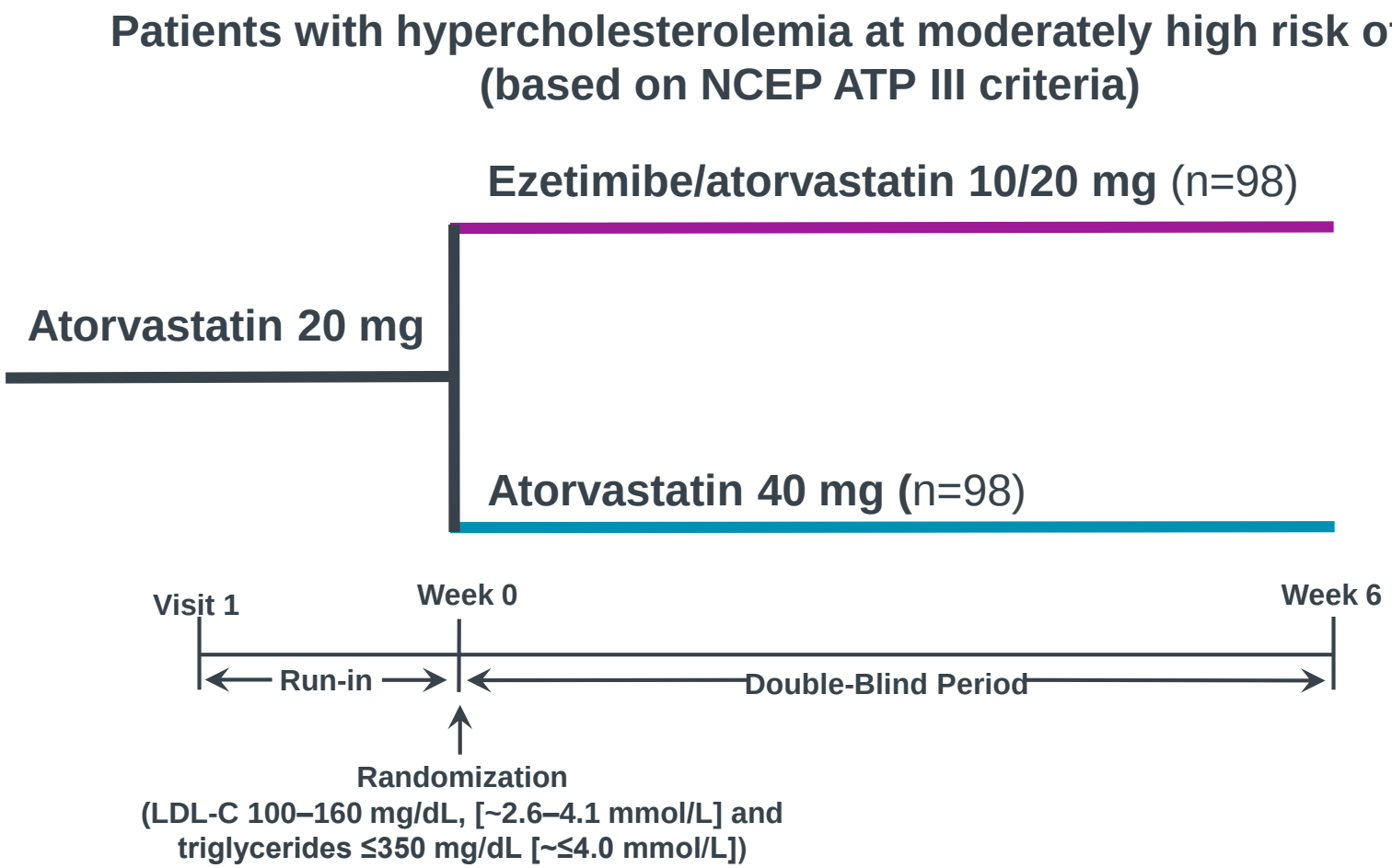
Ezetimibe/Atorvastatin 10/10 mg Provided Significantly Greater LDL-C Reduction Compared With Atorvastatin Monotherapy



Mean baseline LDL-C was 182 mg/dL (~4.7 mmol/L) for ezetimibe/atorvastatin arms (n=255) and 181 mg/dL (~4.7 mmol/L) for atorvastatin arms (n=248).

Ballantyne CM et al. Circulation. 2003;107:2409–2415.

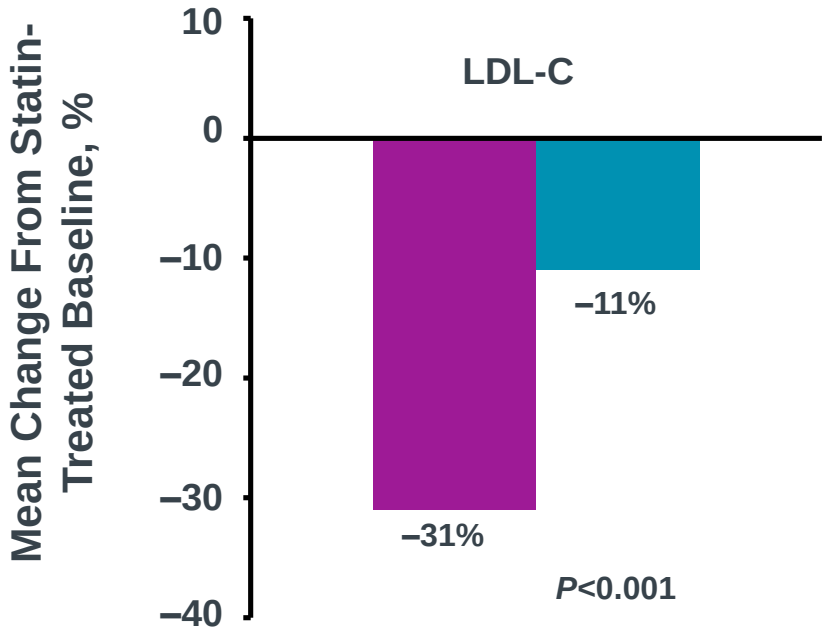
TEMPO: Ezetimibe/Atorvastatin 10/20 mg vs Doubling Atorvastatin Dose to 40 mg (Study Design)[1]



CHD = coronary heart disease; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

1. Conard SE et al. Am J Cardiol. 2008;102:1489–1494.

TEMPO: Ezetimibe/Atorvastatin 10/20 mg Provided Greater Additional LDL-C Reduction vs Doubling Atorvastatin Dose to 40 mg[1]

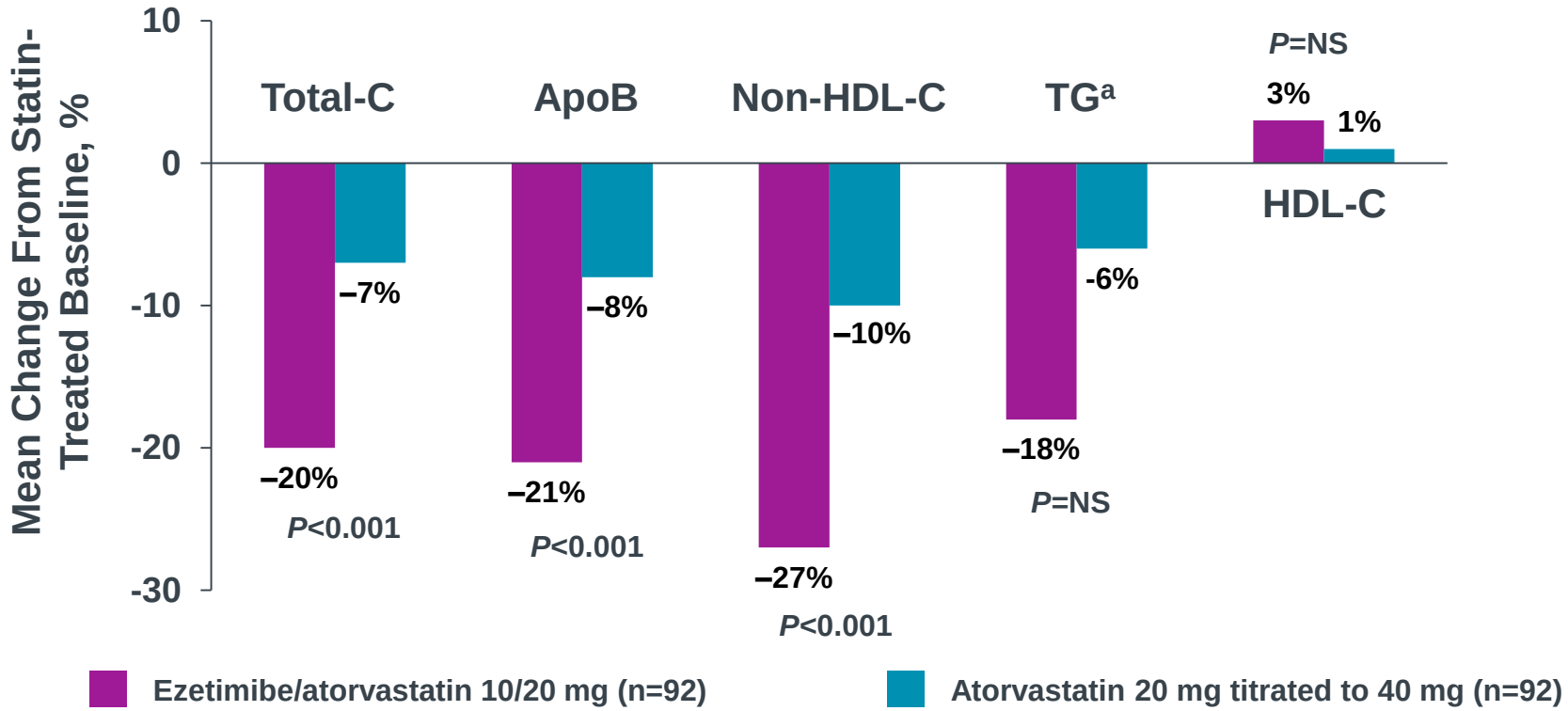


Ezetimibe/atorvastatin 10/20 mg (n=92)
(mean on-statin baseline LDL-C = 120 mg/dL)

Atorvastatin 20 mg titrated to 40 mg (n=92)
(mean on-statin baseline LDL-C = 118 mg/dL)

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

TEMPO: Effect on Multiple Lipid Parameters[1]

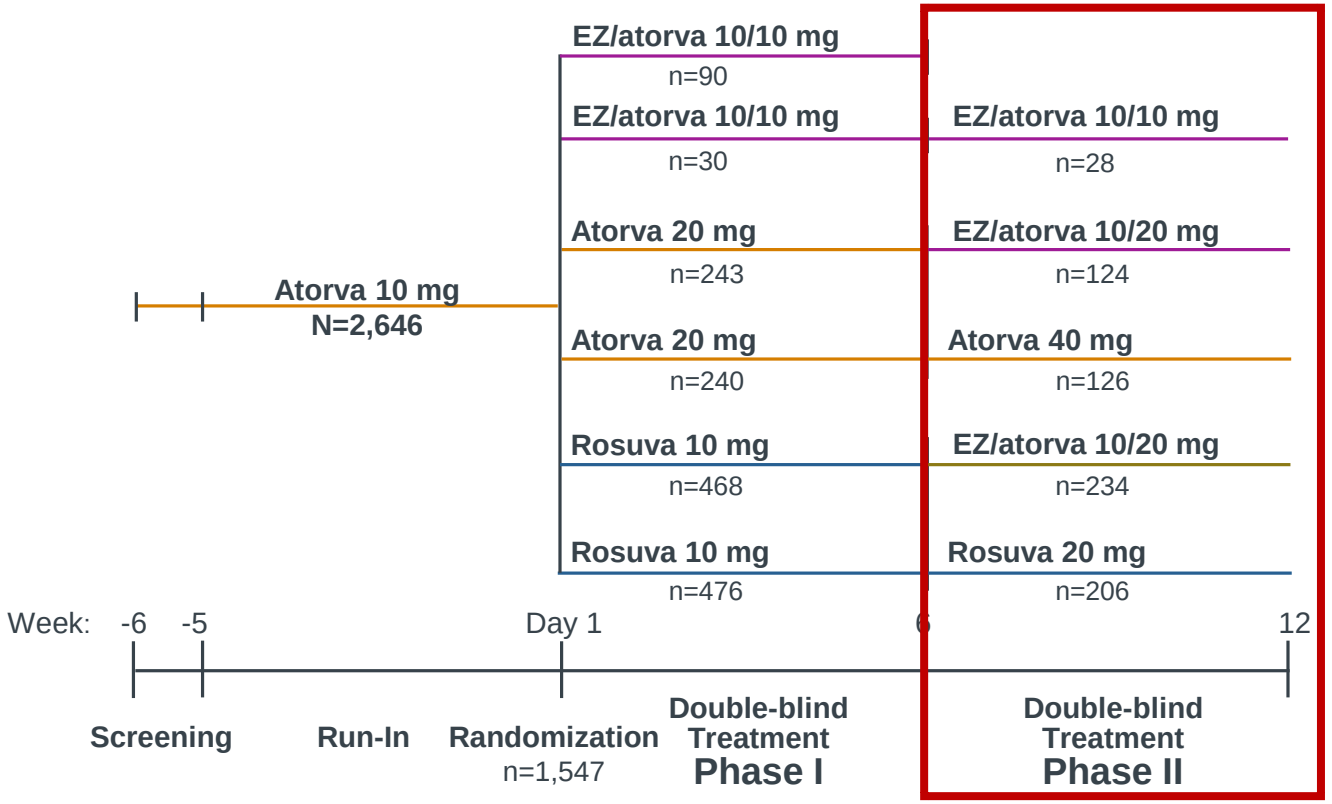


[a]Median change from statin-treated baseline.
NS = not significant.

1. Conard SE et al. *Am J Cardiol*. 2008;102:1489–1494.

PACE:
Efficacy of Ezetimibe/Atorvastatin vs Atorvastatin Uptitration or Switching to Rosuvastatin[1]

High-risk patients[a] with hypercholesterolemia not at LDL-C <100 mg/dL after Phase I



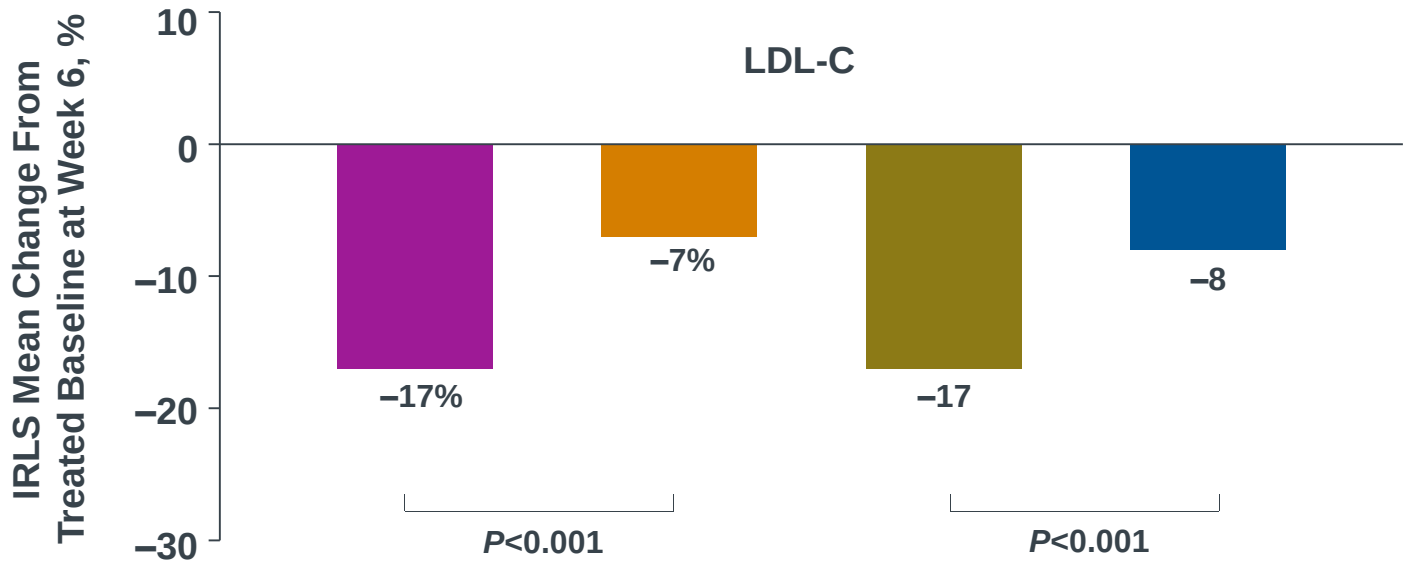
Adapted with permission from Bays HE et al.[1]

[a]High risk of CHD was defined as: 1) subjects without CVD who had type 2 diabetes, or ≥2 risk factors and a 10-year risk for CHD >20% as determined by the Framingham calculation, or 2) subjects with CVD, including established coronary or other atherosclerotic vascular disease.

PACE = a randomized, double-blind, active-controlled, multicenter study of patients with **P**rimary hypercholesterolemia and high cardiovascular risk who are not adequately controlled with **A**torvastatin 10 mg: a **C**omparison of the efficacy and safety of switching to coadministration **E**zetimibe and atorvastatin versus doubling the dose of atorvastatin or switching to rosuvastatin; EZ = ezetimibe; Atorva = atorvastatin; Rosuva = rosuvastatin; CHD = coronary heart disease; CVD = cardiovascular disease.

1. Bays HE et al. Am J Cardiol. 2013;112:1885–1895.

PACE Phase II: Greater Additional LDL-C Reduction With Ezetimibe/Atorvastatin 10/20 mg[1]



Switching from atorvastatin 20 mg to ezetimibe/atorvastatin 10/20 mg (n=124) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)

Doubling atorvastatin to 40 mg (n=124) Mean on-statin baseline LDL-C = 121 mg/dL (~3.1 mmol/L)

Switching from rosuvastatin 10 mg to ezetimibe/atorvastatin 10/20 mg (n=231) Mean on-statin baseline LDL-C = 119 mg/dL (~3.1 mmol/L)

Doubling rosuvastatin to 20 mg (n=205) Mean on-statin baseline LDL-C = 120 mg/dL (~3.1 mmol/L)

IRLS = iteratively reweighted least squares.

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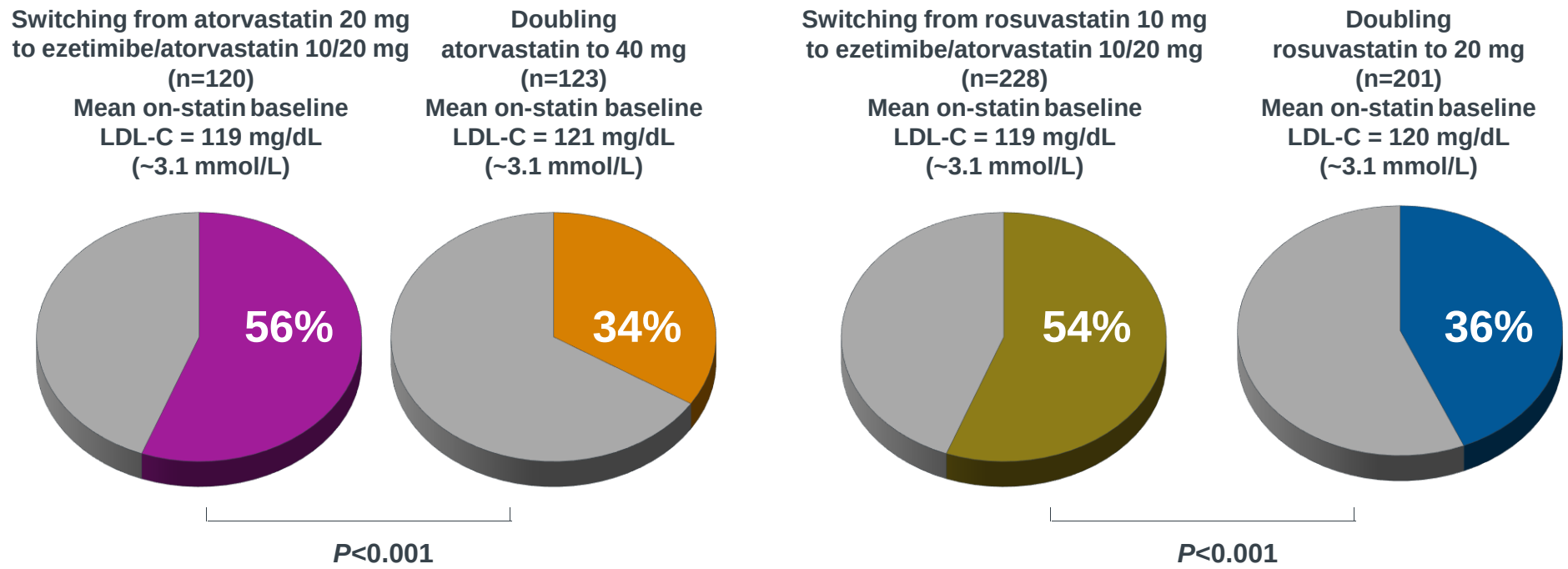
1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895

PACE Phase II: Greater Attainment of LDL-C <100 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

High-risk Patients Reaching LDL-C <100 mg/dL (~2.6 mmol/L) as a Result of Greater LDL-C Reduction



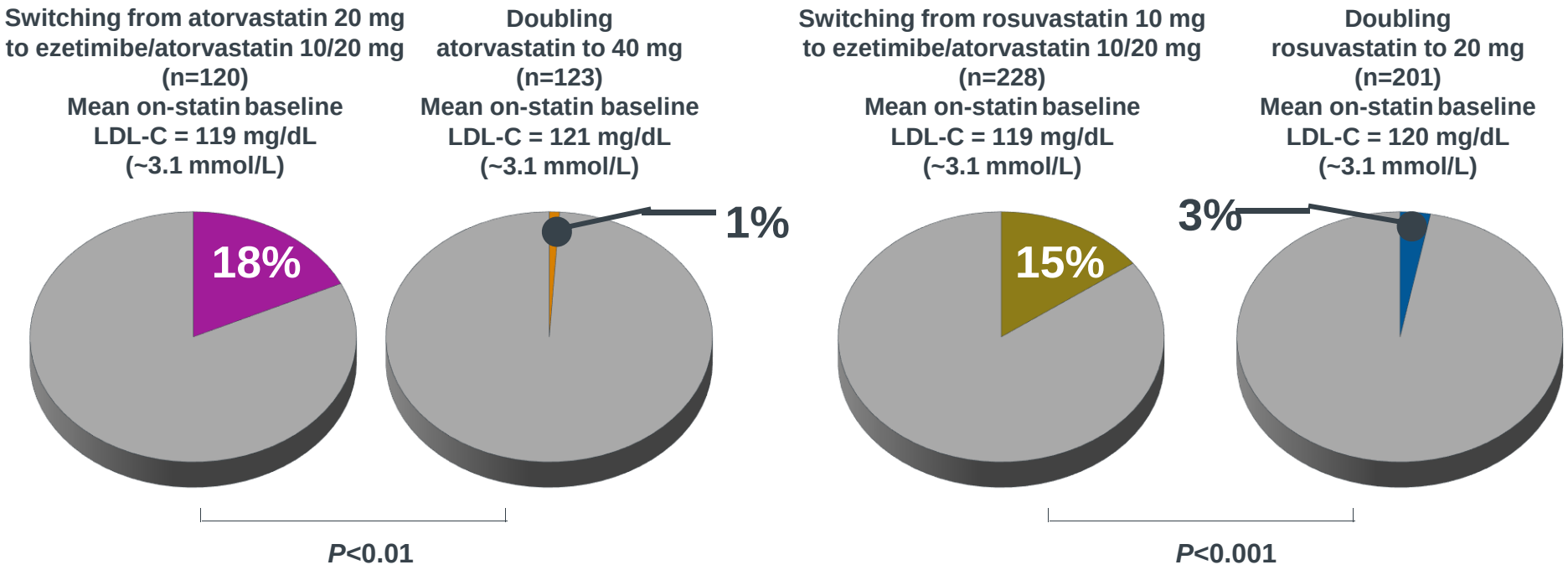
The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

PACE Phase II: Greater Attainment of LDL-C <70 mg/dL With Ezetimibe/Atorvastatin 10/20 mg[1]

High-risk Patients Reaching LDL-C <70 mg/dL (~1.8 mmol/L) as a Result of Greater LDL-C Reduction

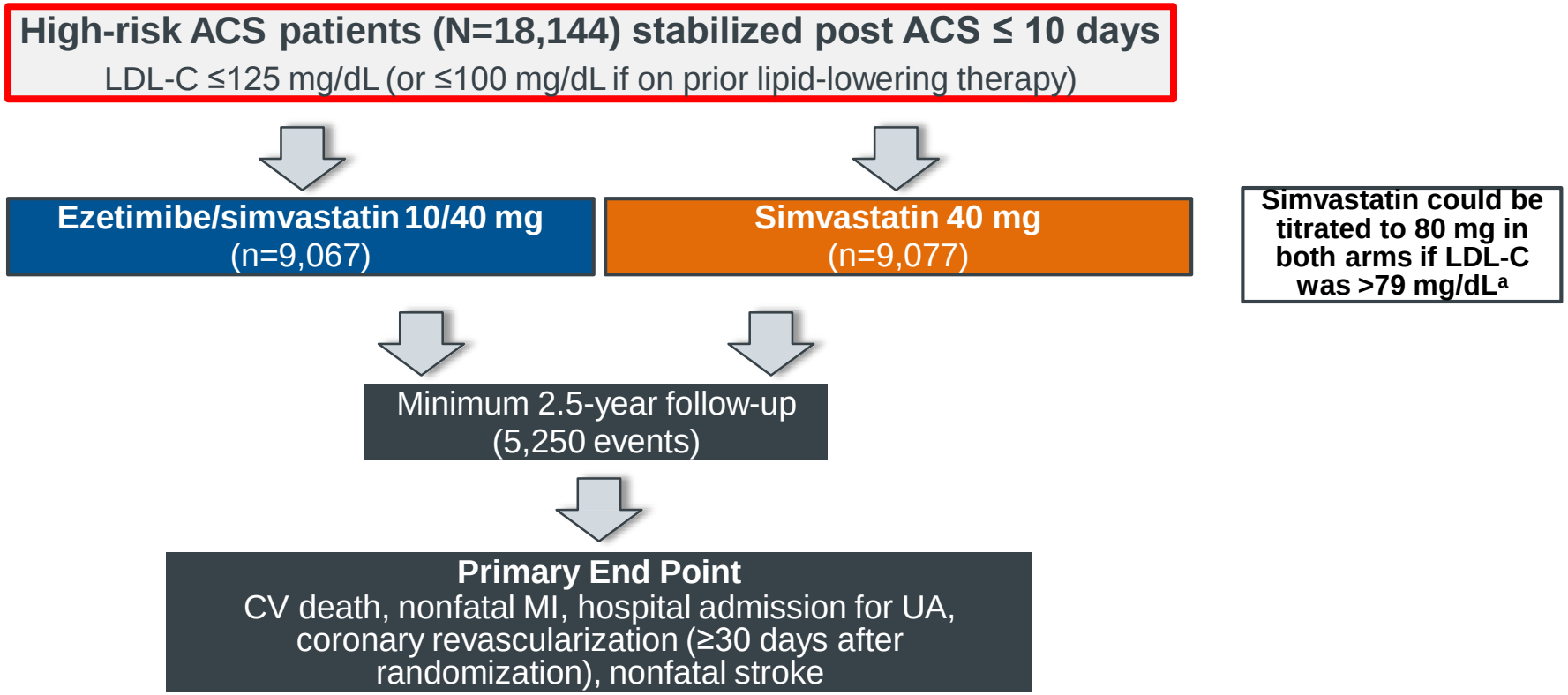


The IRLS mean decrease in LDL-C from statin-treated baseline was 17% with ezetimibe/atorvastatin 10/20 mg compared with 7% with doubling atorvastatin to 40 mg and 17% with ezetimibe/atorvastatin 10/20 mg compared with 8% with doubling rosuvastatin to 20 mg; *P*<0.001 for each comparison.

IRLS = iteratively reweighted least squares

1. Bays HE et al. *Am J Cardiol*. 2013;112:1885–1895.

IMPROVE-IT: Study Design[1-3]



Adapted with permission from Cannon CP et al.[1]

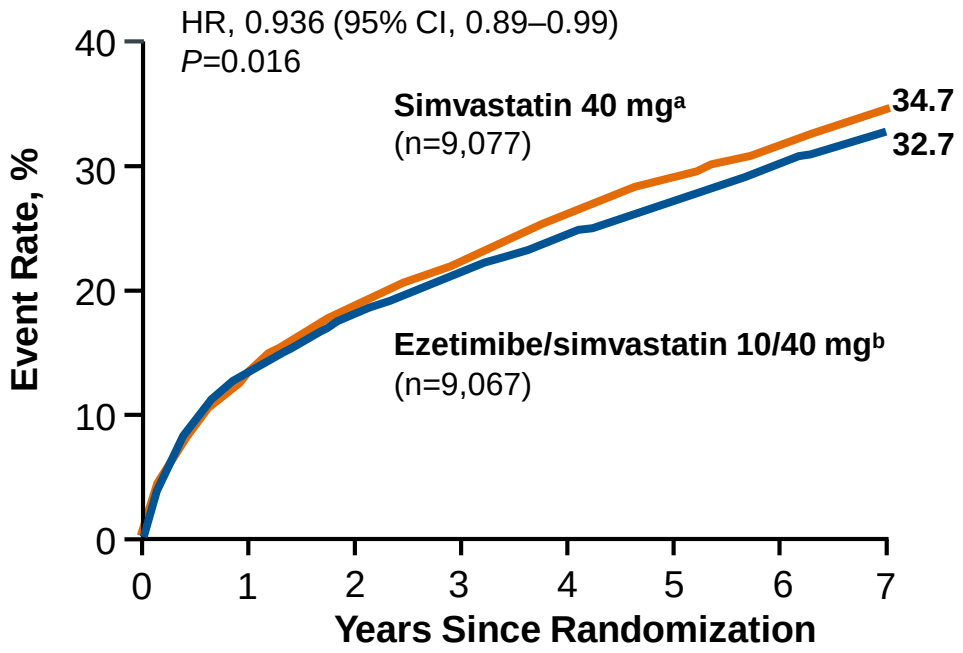
[a]Titration stopped per June 2011 protocol amendment.[2]

IMPROVE-IT = Improved Reduction of Outcomes: Vytorin Efficacy International Trial; ACS = acute coronary syndrome; CV = cardiovascular; MI = myocardial infarction; UA = unstable angina.

1. Cannon CP et al. *Am Heart J*. 2008;156:826–832. **2.** Blazing MA et al. *Am Heart J.* 2014;168:205–212.e1. **3.** Cannon CP et al. *N Engl J Med*. 2015;372:2387–2397.

IMPROVE-IT: Ezetimibe + Statin Improved CV Outcomes Beyond a Statin Alone[1]

Ezetimibe/simvastatin significantly reduced CV events more than simvastatin alone



Primary End Point

CV death, nonfatal MI, hospital admission for UA, coronary revascularization (≥30 days after randomization), or nonfatal stroke

Used with permission from Cannon CP et al.[1]

[a]27% were uptitrated to simvastatin 80 mg.

[b]6% were uptitrated to ezetimibe/simvastatin 10/80 mg.

CV = cardiovascular; HR = hazard ratio; CI = confidence interval; RRR = relative risk reduction; MI = myocardial infarction; UA = unstable angina.

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

IMPROVE-IT : Ezetimibe added to statin therapy after acute coronary syndromes, specified subgroup in DM

Circulation

American Heart Association®

Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT

Robert P. Giugliano, Christopher P. Cannon, Michael A. Blazing, Jose C. Nicolau, Ramon Corbalan, Jindrich Spinar, Jeong-Gun Park, Jennifer A. White, Erin Bohula and Eugene Braunwald
on behalf of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators

Circulation. published online December 20, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

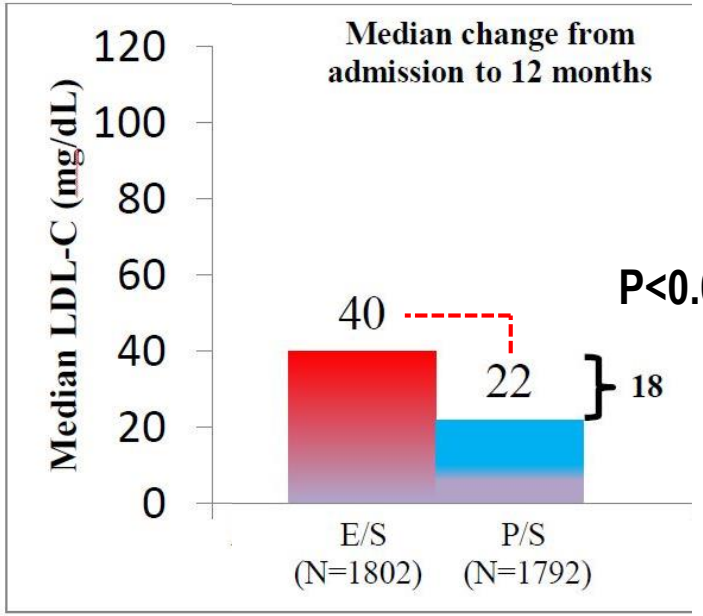
Print ISSN: 0009-7322. Online ISSN: 1524-4539

Giugliano et al.; Circulation. 2018;137:1571–1582

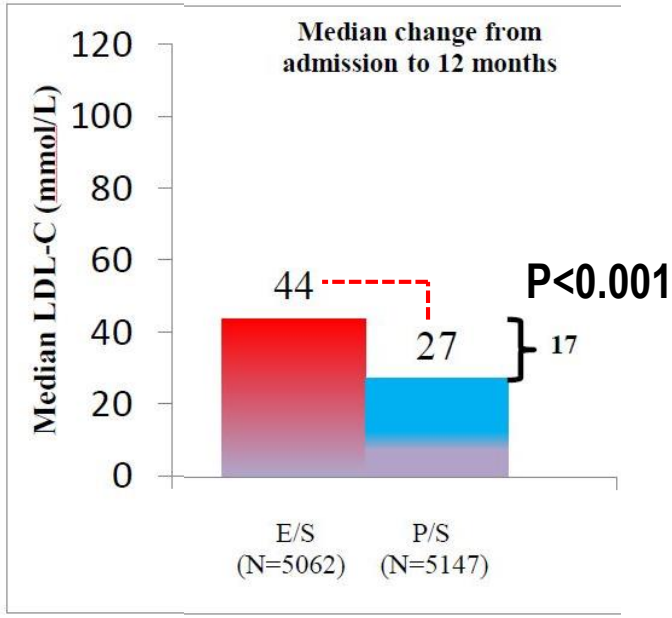
Mean changes in LDL-C from admission at 12 months

The resultant median difference in LDL-C reduction from admission to year 1 in patients without DM between treatments of 17 mg/dL was similar to that observed in patients with DM (18 mg/dL, P interaction =0.58).

With diabetes mellitus



Without diabetes mellitus

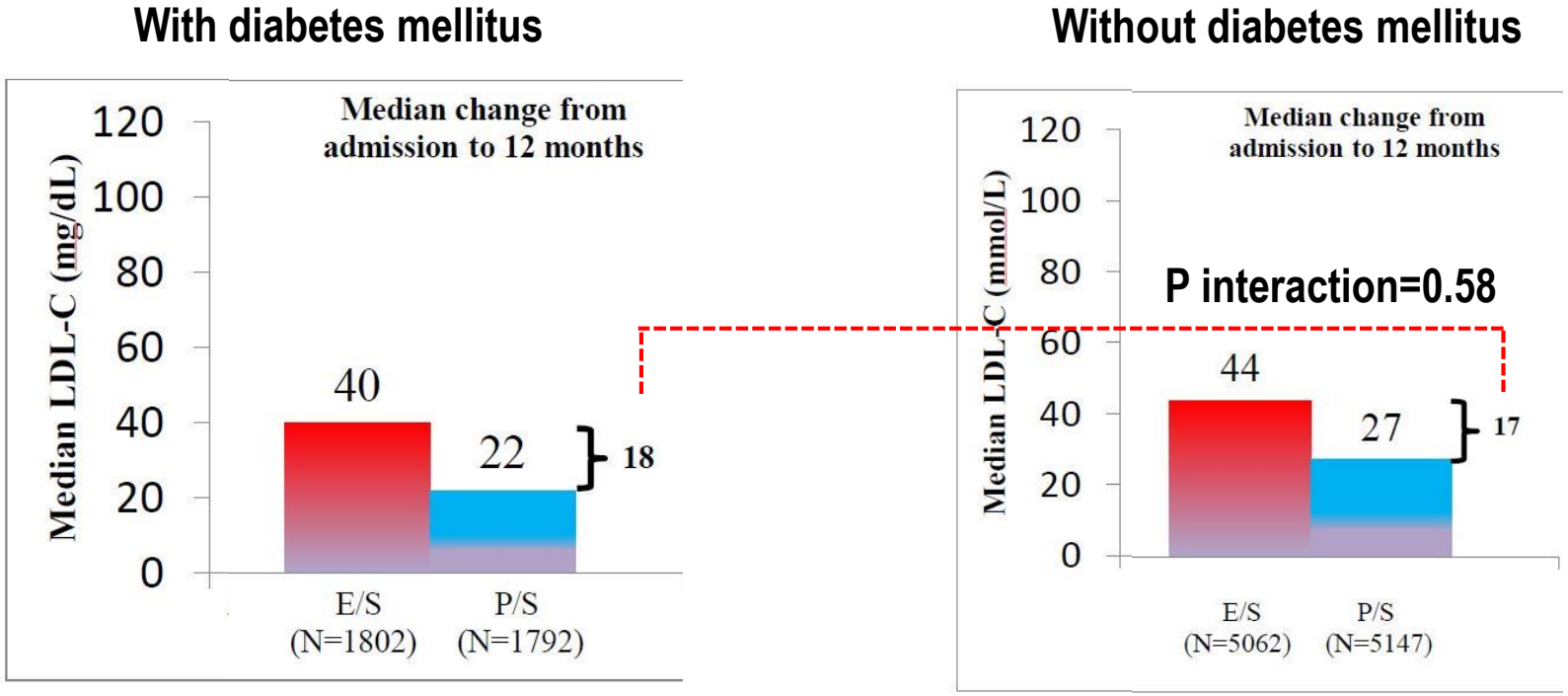


Median LDL-C at admission and 12 months in patients with and without diabetes mellitus

Giugliano et al.; Circulation. 2018;137:1571–1582

Mean changes in LDL-C from admission at 12 months

Patients treated with E/S as compared to P/S, also achieved greater reductions in total cholesterol, triglycerides, and non-HDL-C during the trial both among patients with and without DM. **(P interaction=0.58)**

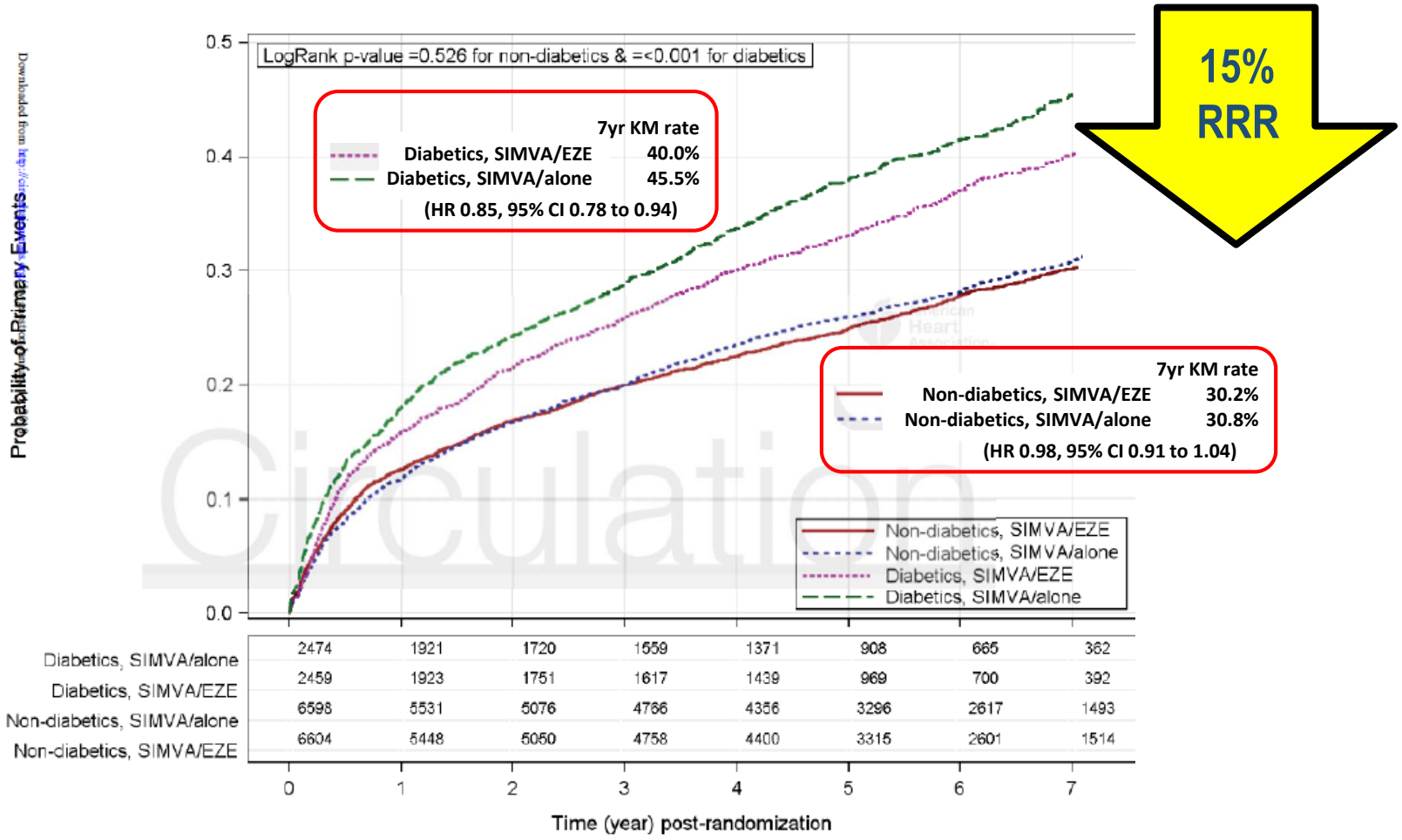


Median LDL-C at admission and 12 months in patients with and without diabetes mellitus

Giugliano et al.; Circulation. 2018;137:1571–1582

Kaplan-Meier curves for the primary efficacy endpoint

primary composite endpoint of cardiovascular death, major coronary event (nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization occurring > 30 days post randomization), or nonfatal stroke



Giugliano et al.; Circulation. 2018;137:1571–1582

在第二型糖尿病的病人，使用eze+simva可以顯著降低主要心血管事件的發生。主要來自於降低心肌梗塞（MI）和缺血性腦中風（ischemic stroke）

Individual cardiovascular endpoints and CVD/MI/stroke

		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	

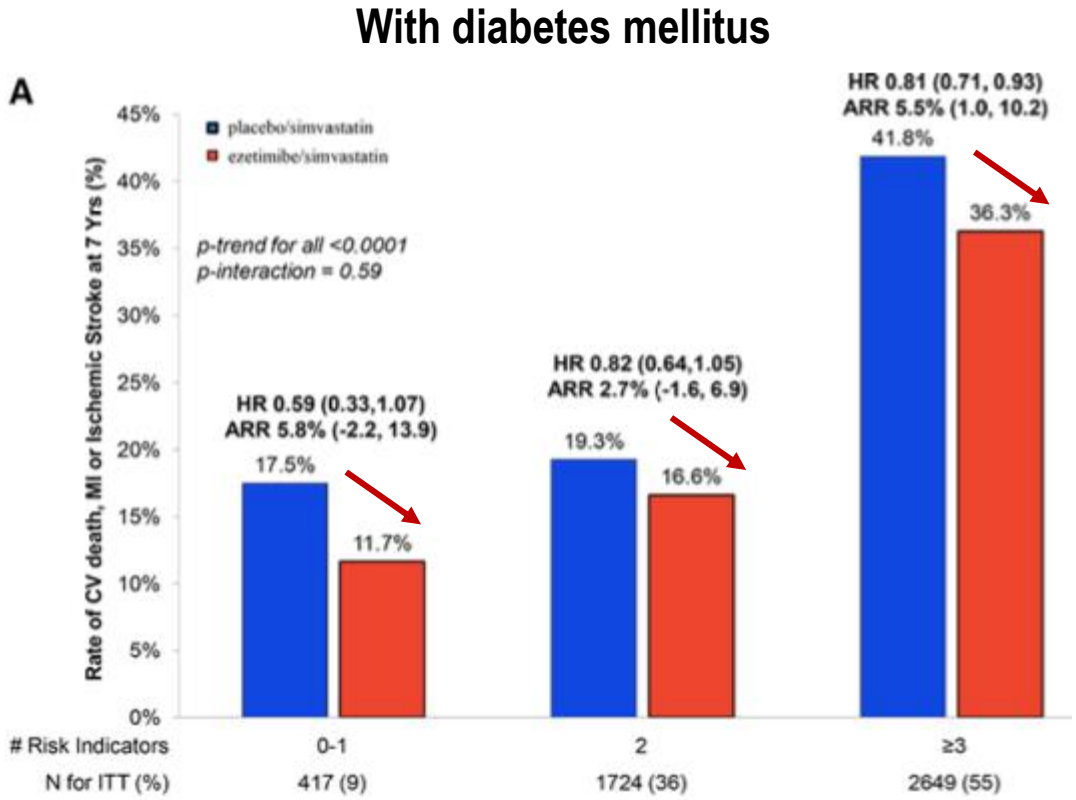
(By Kaplan-Meier event rates at 7 years analysis)

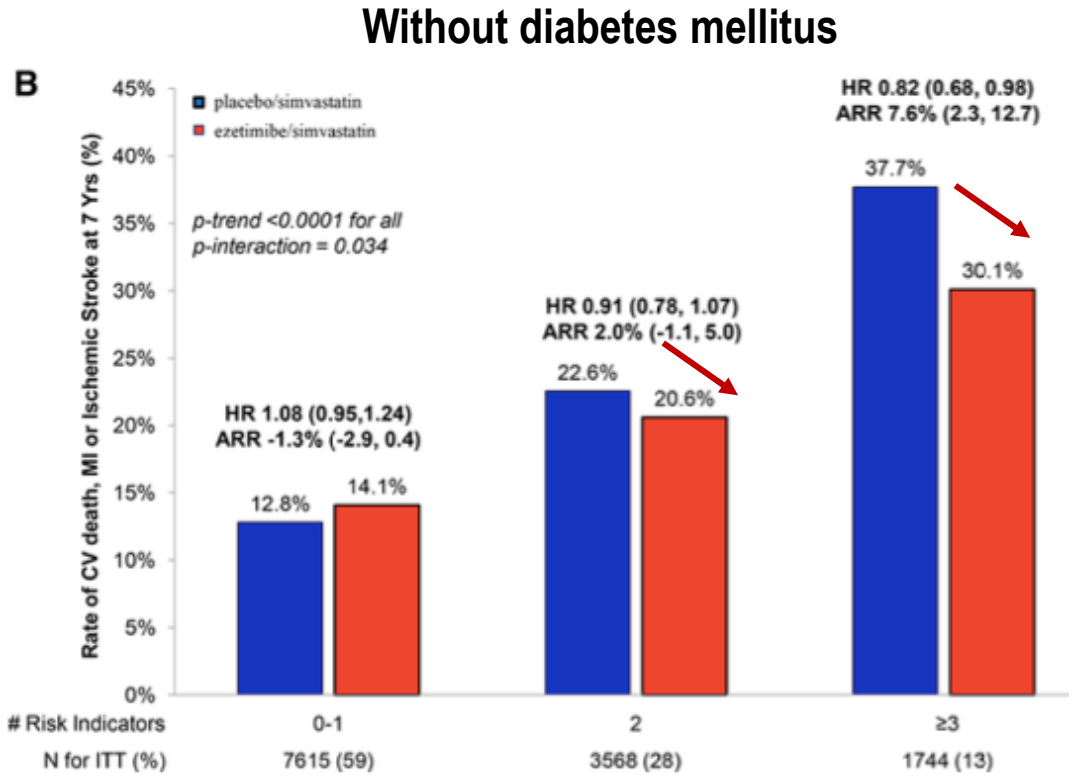
Giugliano et al.; Circulation. 2018;137:1571–1582

Risk stratification and outcomes in patients with and without DM

In patients with DM, the benefit of E/S over P/S in reducing the composite of cardiovascular death, MI, and ischemic stroke was consistent across the risk strata

In patients without DM, there was significant effect modification by the risk score (P interaction 0.034), with non-diabetics at high risk experiencing a significant 18% reduction with E/S compared to P/S .





Giugliano et al.; Circulation. 2018;137:1571–1582

總結

- Dyslipidemia is a major cause of increase cardiovascular risk worldwide, it is therefore important to treat aggressively and LDL-C remains the primary target of therapy.

- Recent guidelines recommended aggressive lipid-lowering treatment to reduce cardiovascular events in high cardiovascular risk patients

- Statin is the primary choice to reduce LDL-C. For those not reaching treatment target despite statin, combination with ezetimibe can further lower LDL-C level.

- Fixed dose combination of atorvastatin and ezetimibe improved drug adherence and can reduce pills number.


Thank You