Establish the Standard of Care for Dyslipidemia Treatment on High-risk Patients

Date: 2020/07/19

Time: 09:40-10:15 (35 min)

Speaker: 彰化基督教醫院 心臟血管內科 楊淵博

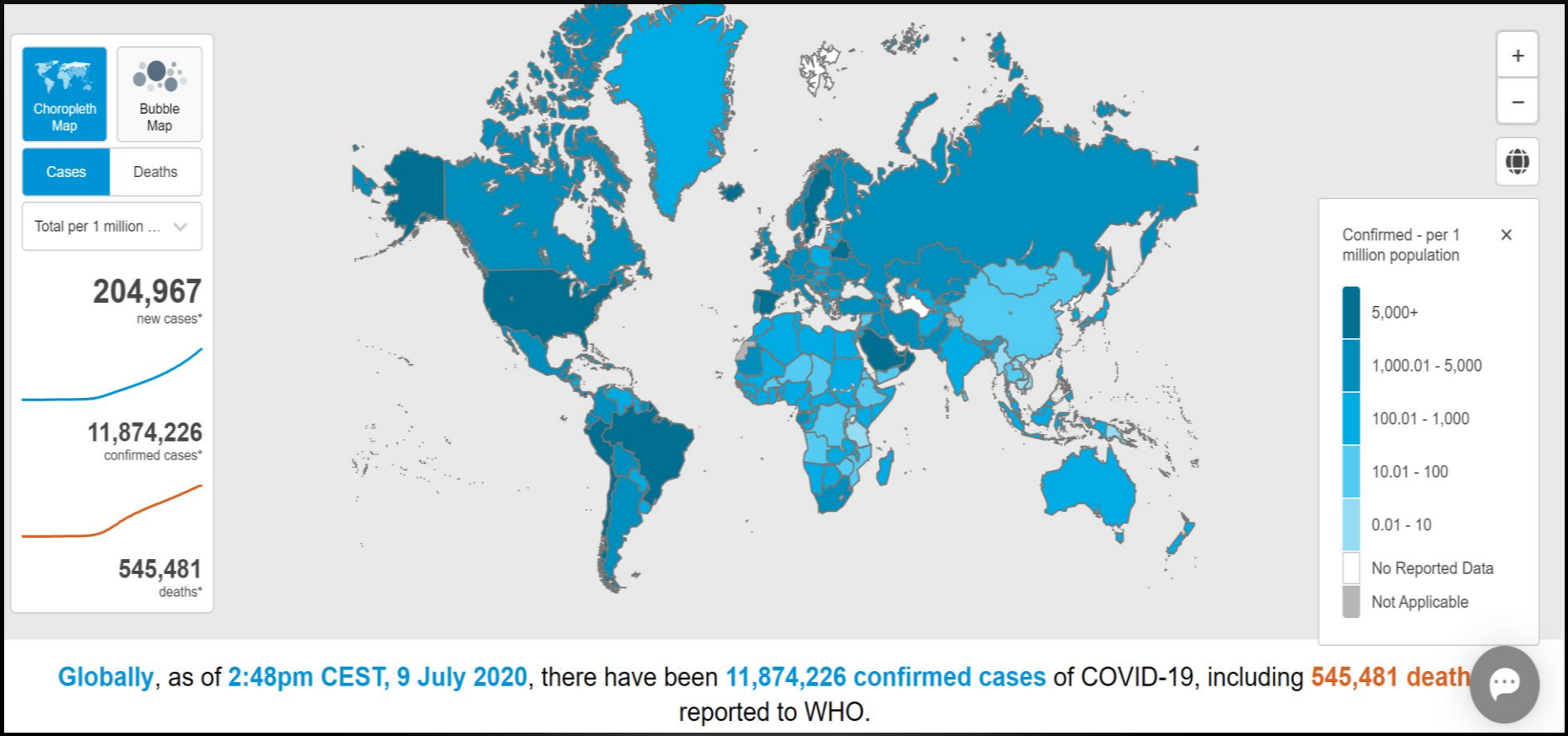
Moderator: 陳文鍾 榮譽理事

今天這場演講

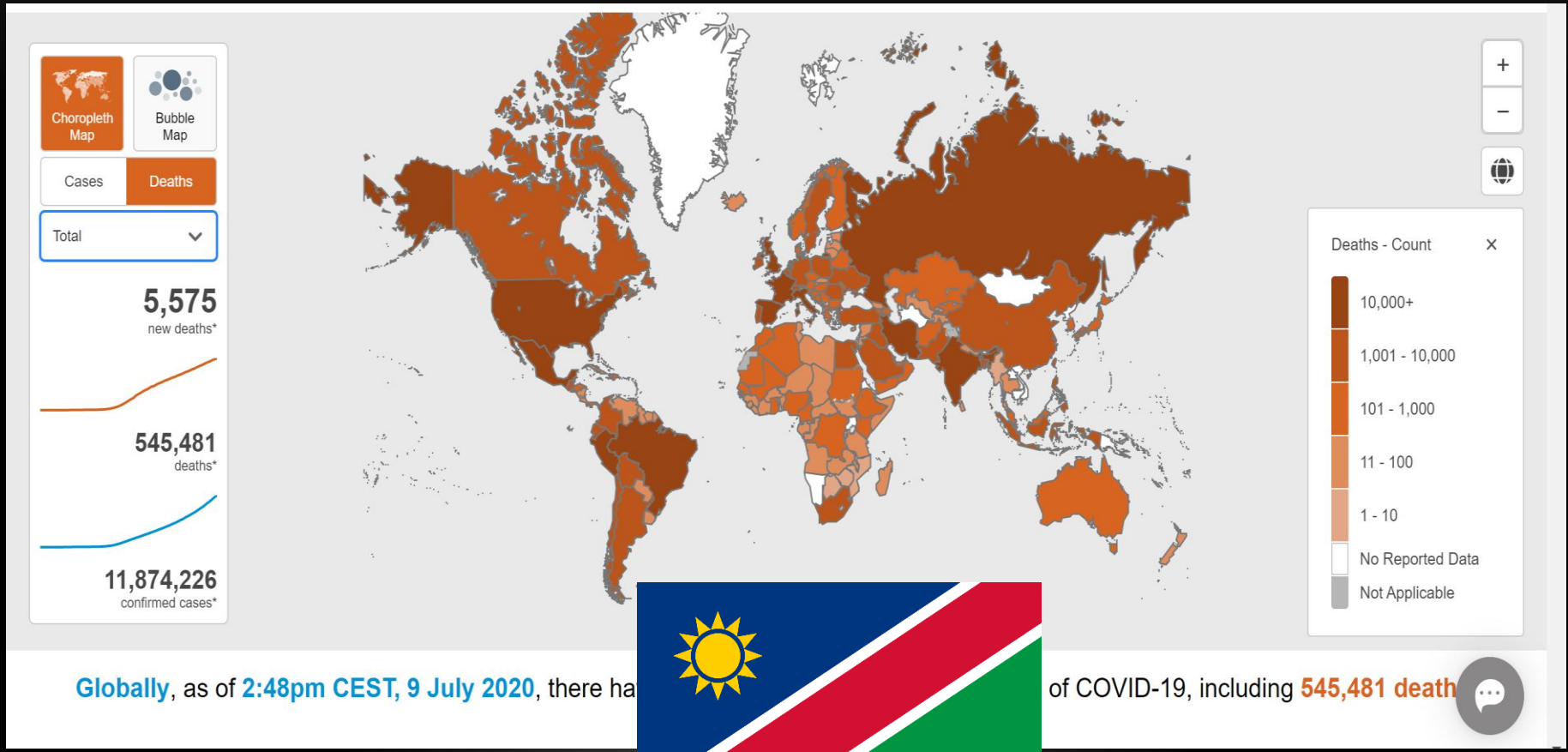
- 開放
- 錄音
- 錄影
- 拍照

COVID-19
(Update; 2020/07/10)

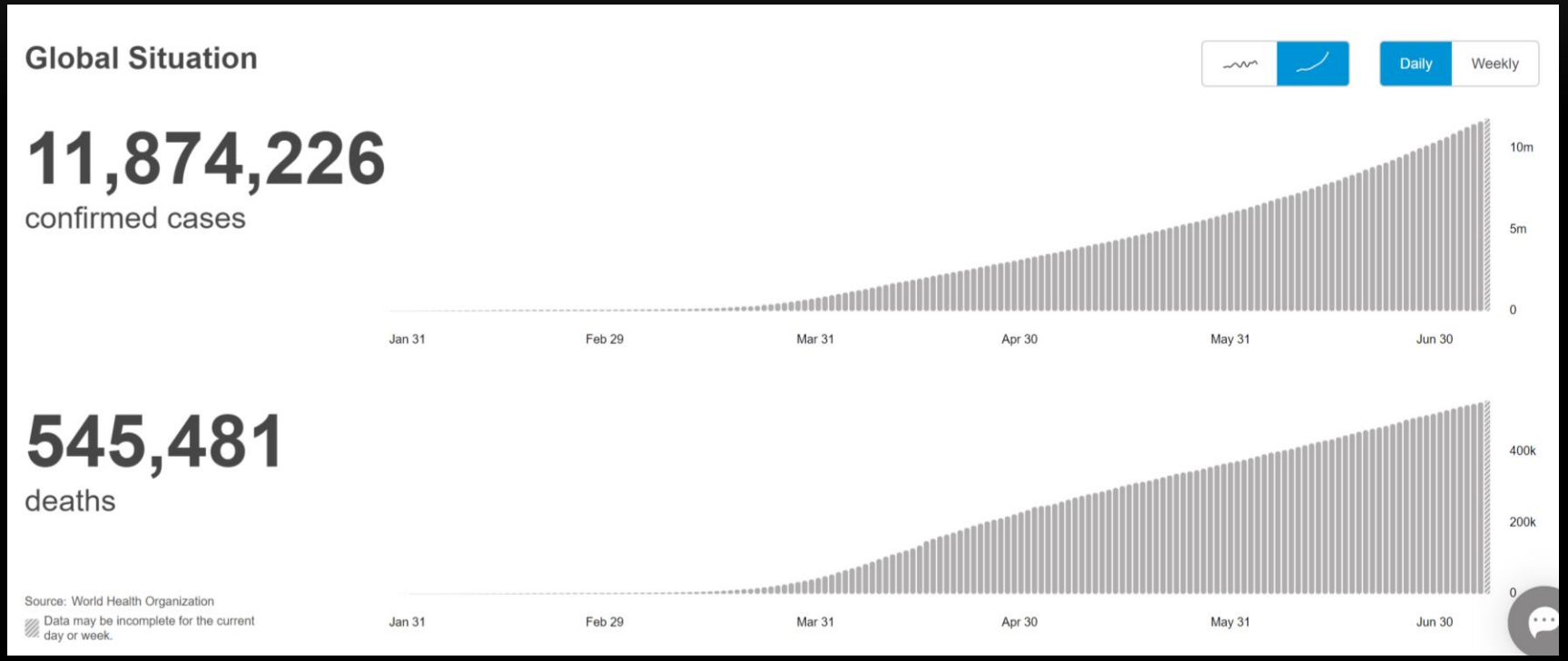
WHO Website


Choropleth Map
Bubble Map
Cases
Deaths
Total per 1 million ...
204,967
new cases*
11,874,226
confirmed cases*
545,481
deaths*
+
−
Confirmed - per 1 million population
5,000+
1,000.01 - 5,000
100.01 - 1,000
10.01 - 100
0.01 - 10
No Reported Data
Not Applicable
Globally, as of 2:48pm CEST, 9 July 2020, there have been 11,874,226 confirmed cases of COVID-19, including 545,481 death
reported to WHO.

WHO Website (外蒙/納米比亞)



WHO Website

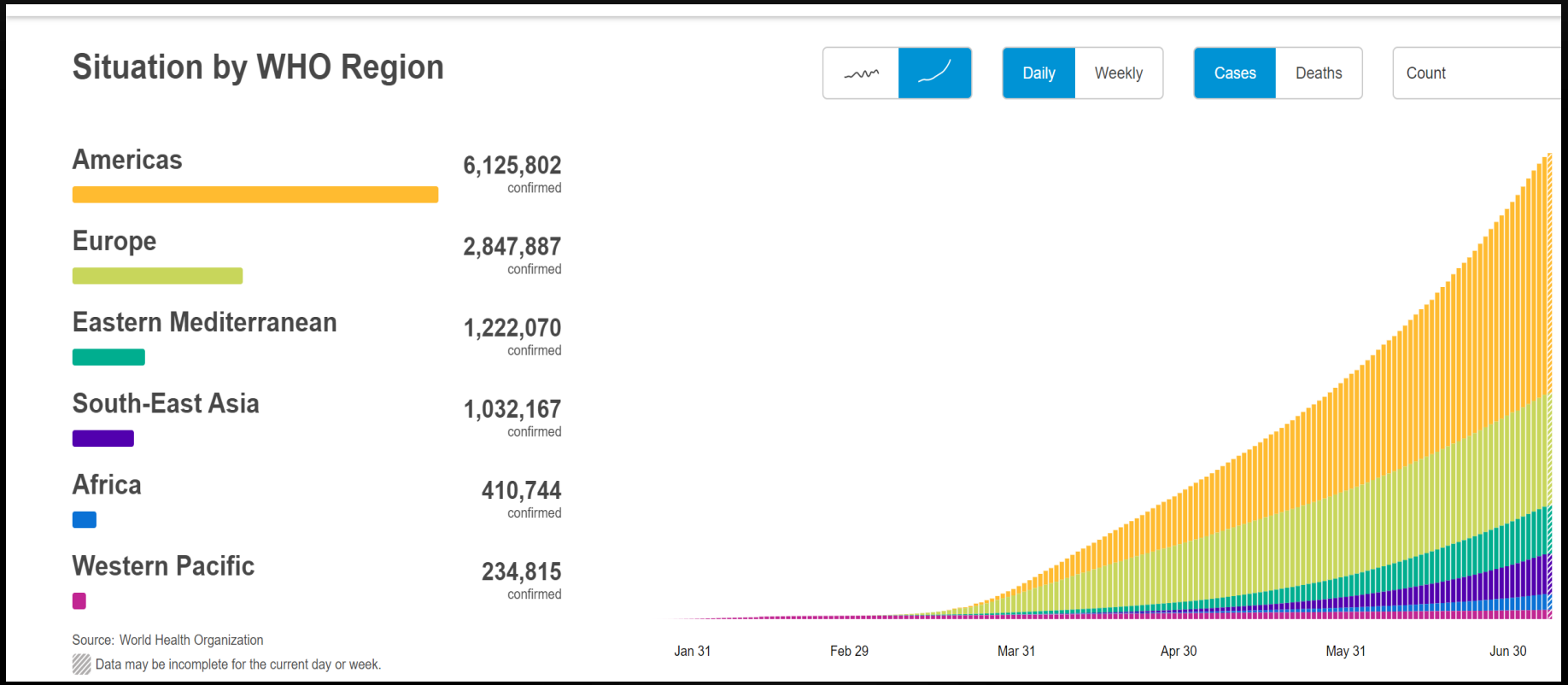


From WHO

Fatality Rate

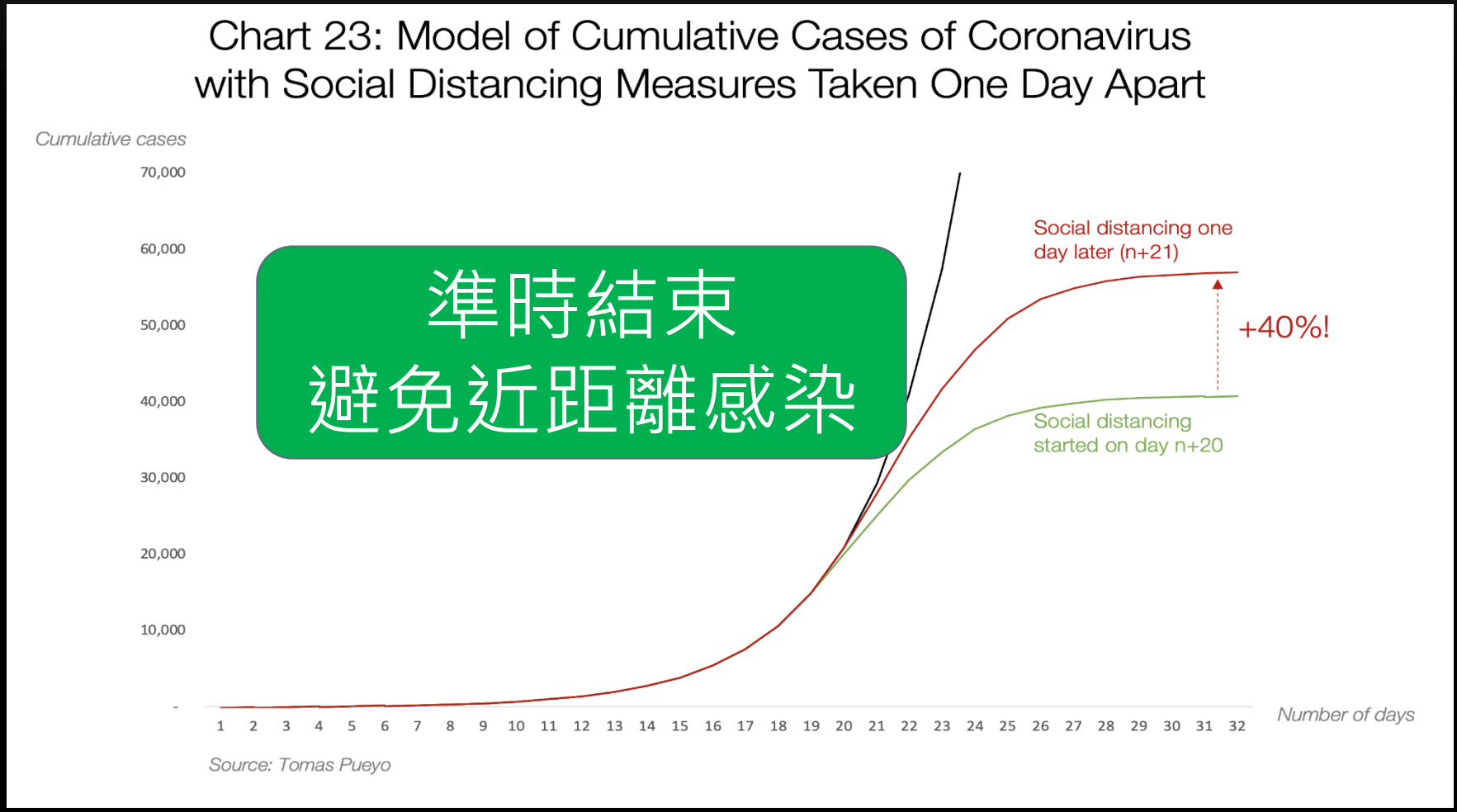
- From WHO Data (until 2020/07/09)
  - Total: 11,874,226
  - Death: 545,481
  - Fatality Rate: **4.5%**

Update of COVID-19



From Google

Cumulative Cases if Isolation



林維文醫師

- For high/very-high risk patient, LDL should be controlled under
- JUPITOR Trial
  - Rosuvastatin is a good medication for health human
  - High potency statin
  - ↓ Atheroma plaque, ↓ CV events, ↓ Ischemia stroke

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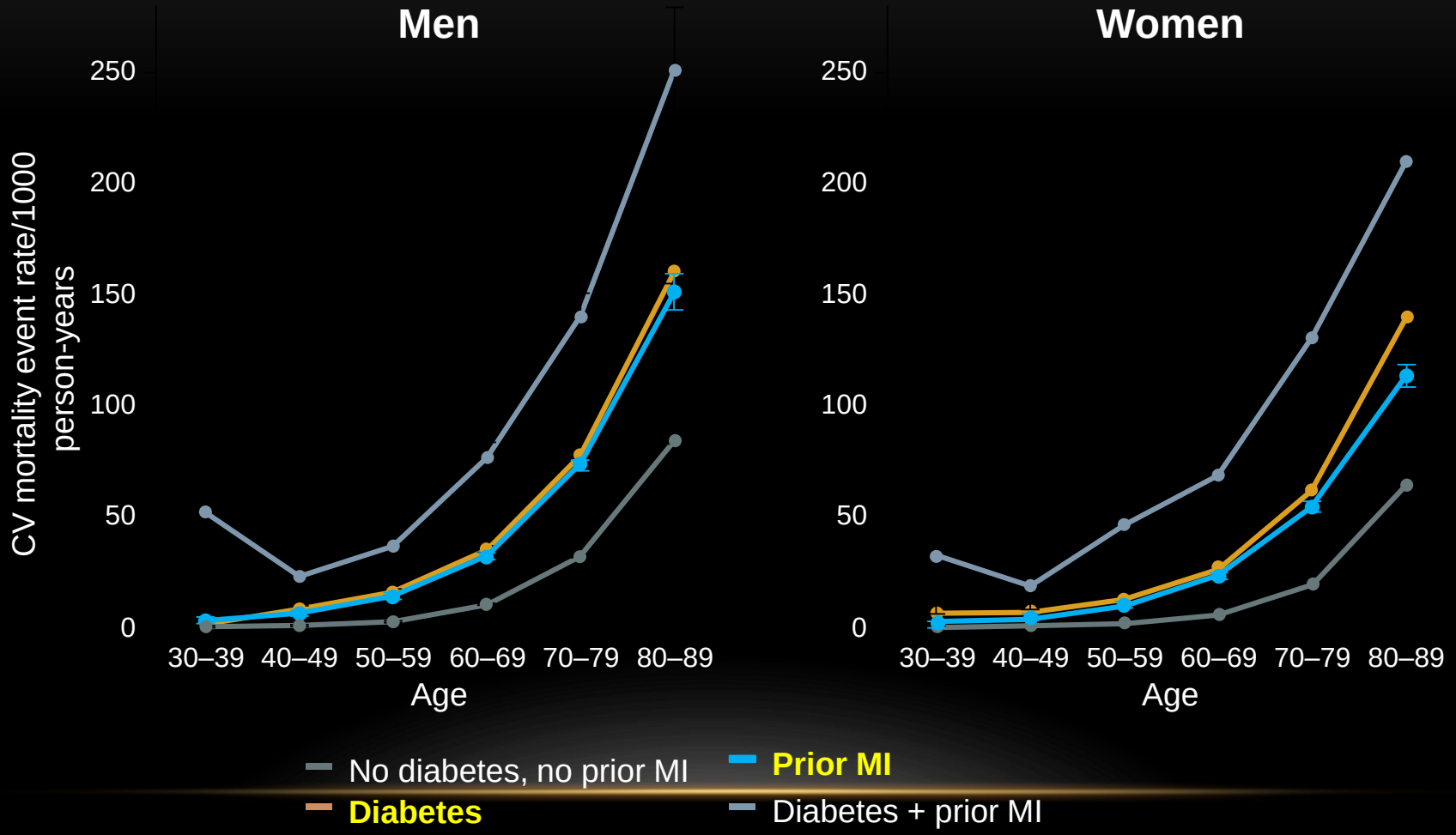
High Risk Patients

High Risk Patients

DM and AMI (Danish Civil Registration)



Circulation 2008;117:1945–54.

In Clinical Trials (Lowering Lipid %, n)

LEADER
(Liraglutide)

N Engl J Med 2016; 375:311-322

EMPA-REG
(Empaglifozin)

N Engl J Med 2015; 373:2117-2128

CARMELINA
(Linagliptin)

JAMA. 2019;321(1):69-79

CREDENCE
(Canaglifozin)

Circulation. 2019;140:739–750

In Clinical Trials (Lowering Lipid %, n)

LEADER
(Liraglutide)

75%

N Engl J Med 2016; 375:311-322

EMPA-REG
(Empaglifozin)

80%

N Engl J Med 2015; 373:2117-2128

CARMELINA
(Linagliptin)

72%

JAMA. 2019;321(1):69-79

CREDENCE
(Canaglifozin)

70%

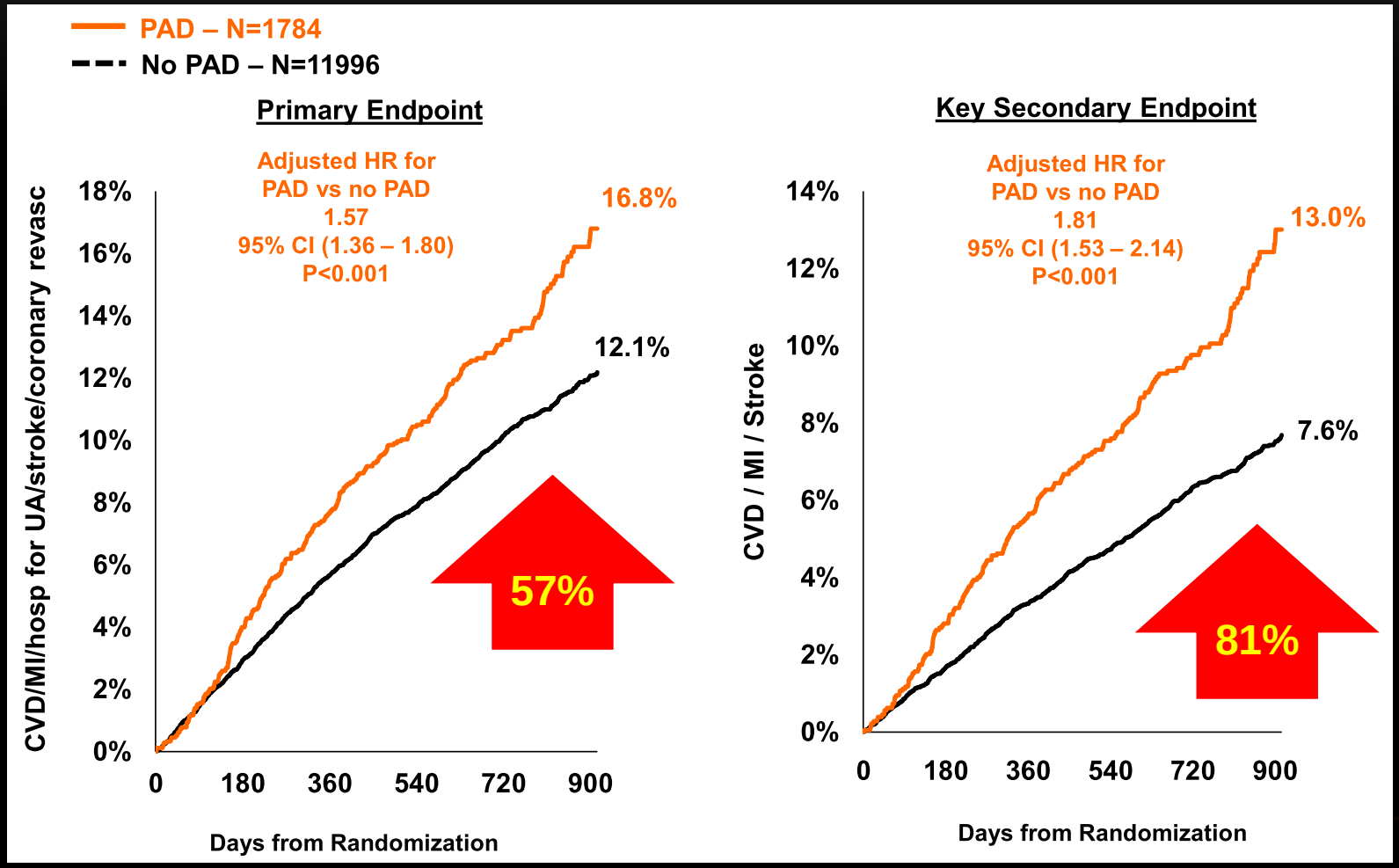
Circulation. 2019;140:739–750

PAD & DM


4月25日
4月23日
4月2日
3月22日
3月20日
3月13日
3月7日
2015年4月8日
2015年3月17日
2014年8月14日
2014年7月31日
2014年7月30日
2014年7月27日
2014年7月24日
2014年7月14日
2014年7月11日
2014年7月4日
25734587
15131948

Hazard Ratio of PAD/no PAD

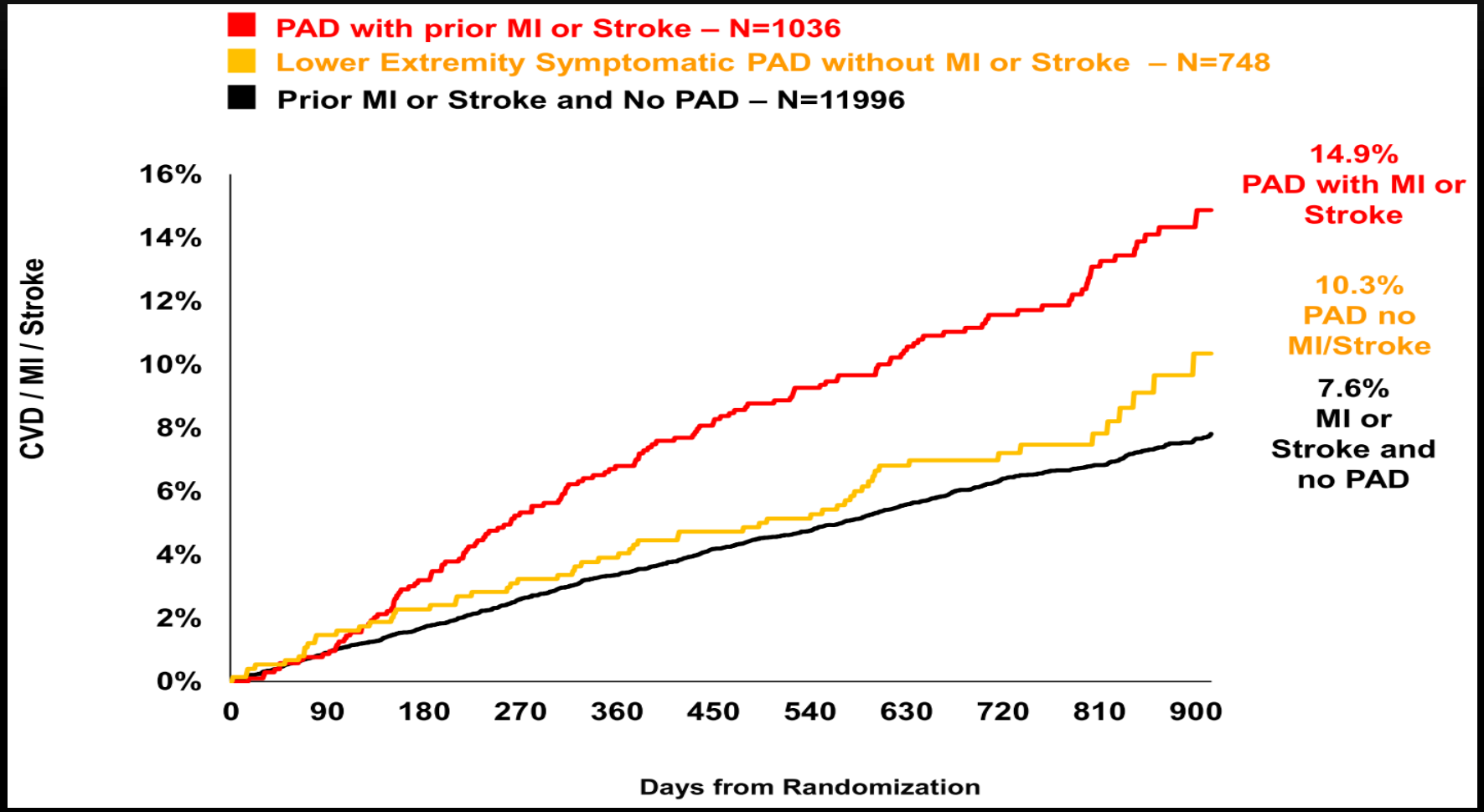
(FOURIER Study)



Circulation. 2018;137:338–350

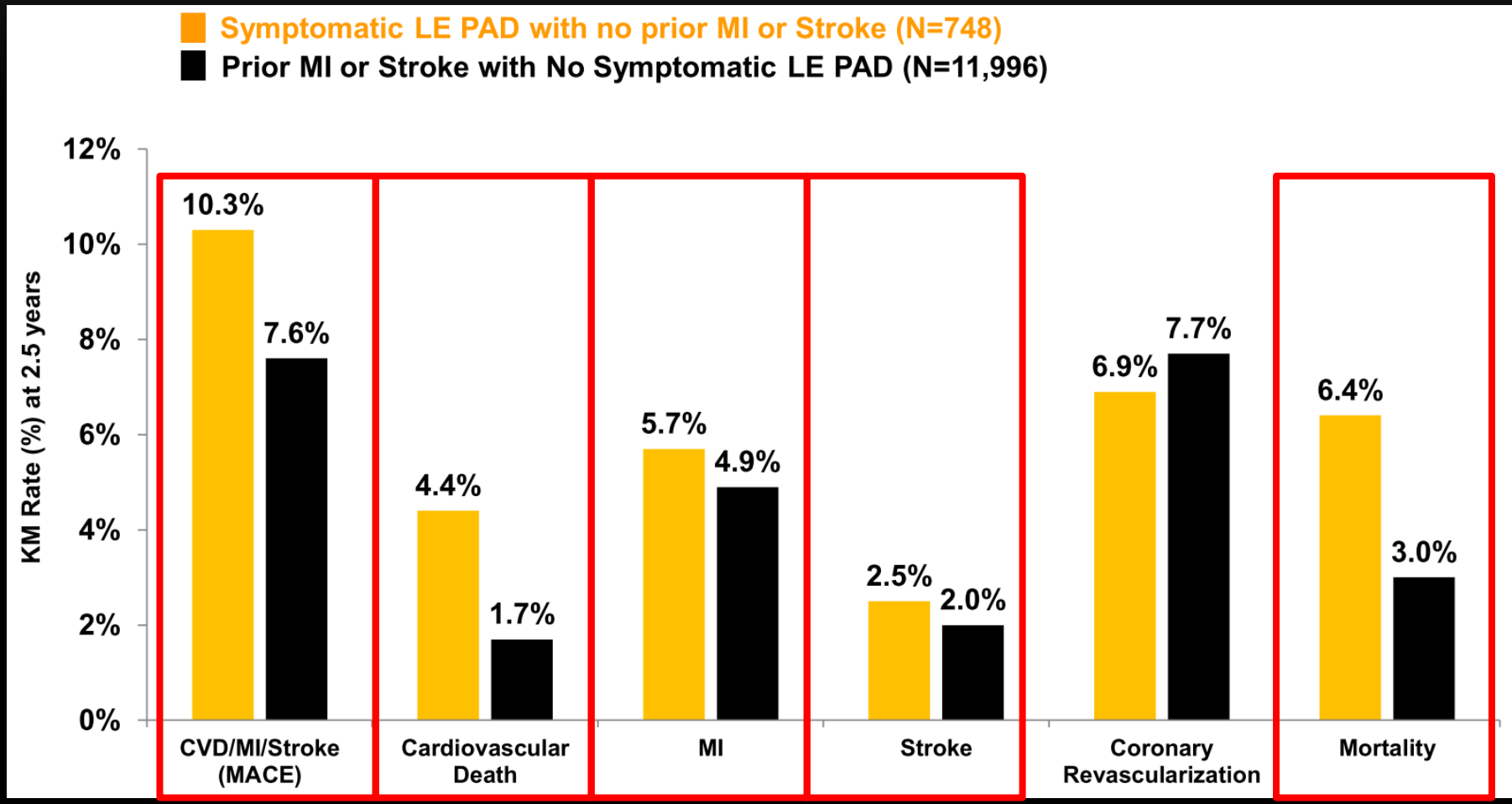
CVD(MI/Stroke)/PAD

(FOURIER Study)



Circulation. 2018;137:338–350

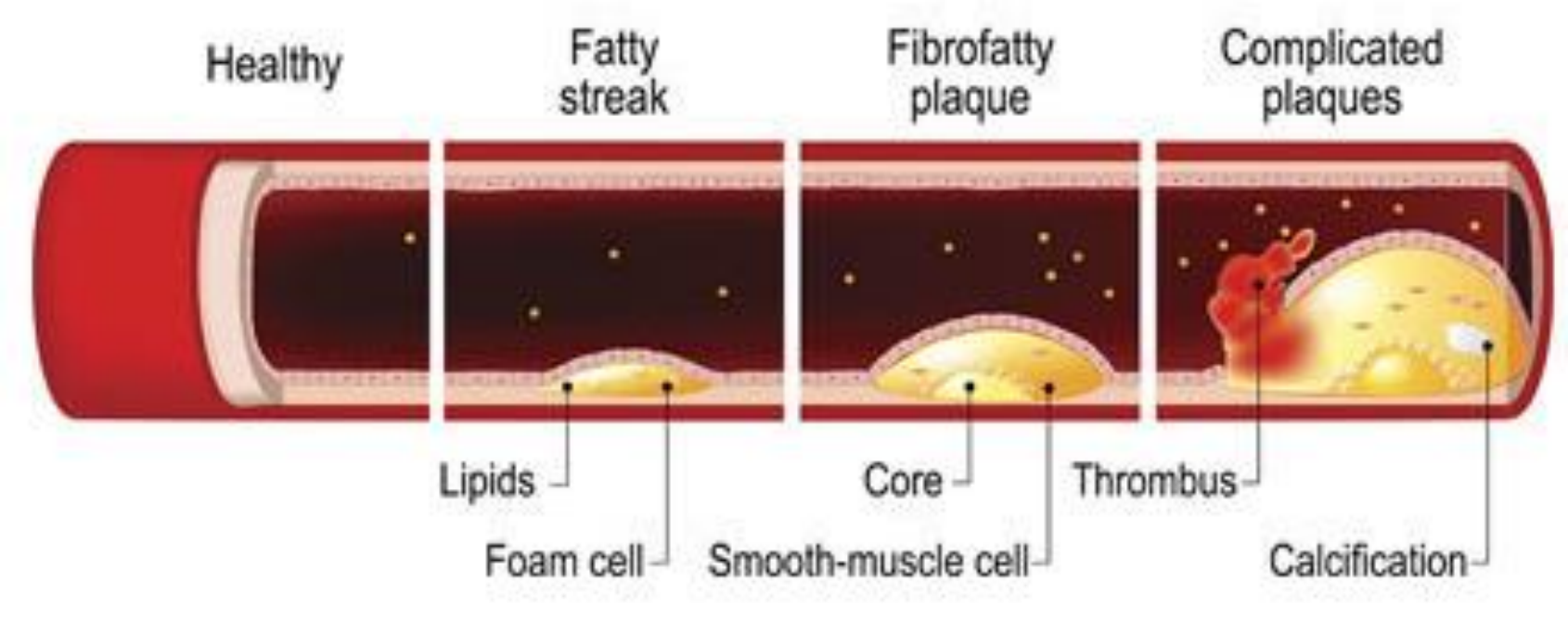
MACE in Placebo Patients



Circulation. 2018;137:338–350

ASCVD

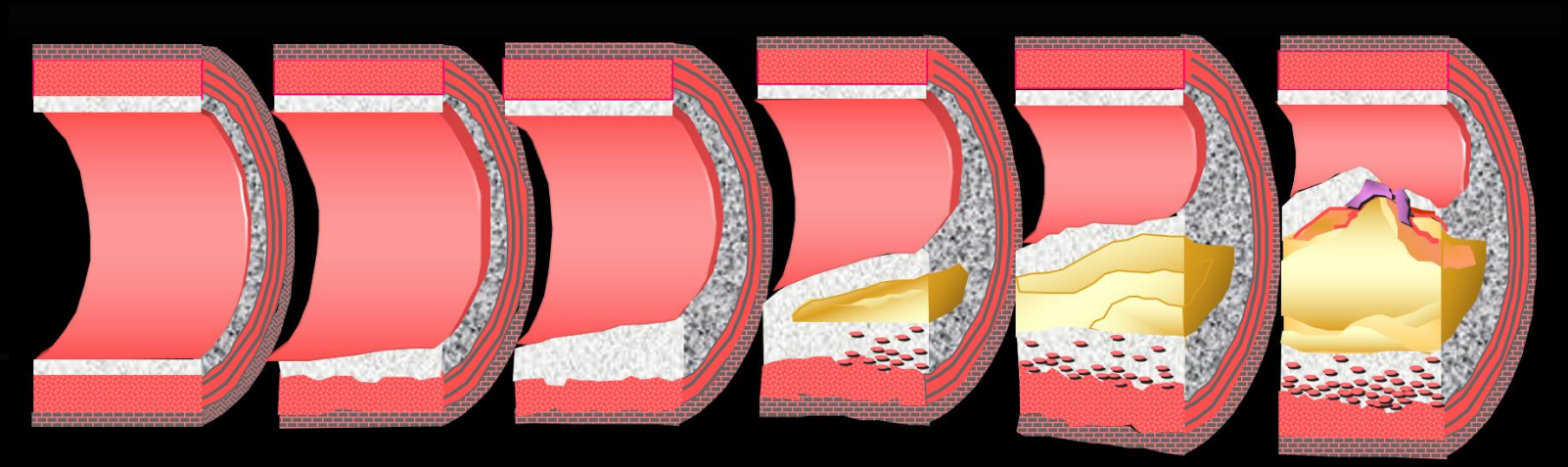
- **ASCVD**
  Athero**S**clerotic **C**ardio**V**ascular **D**isease



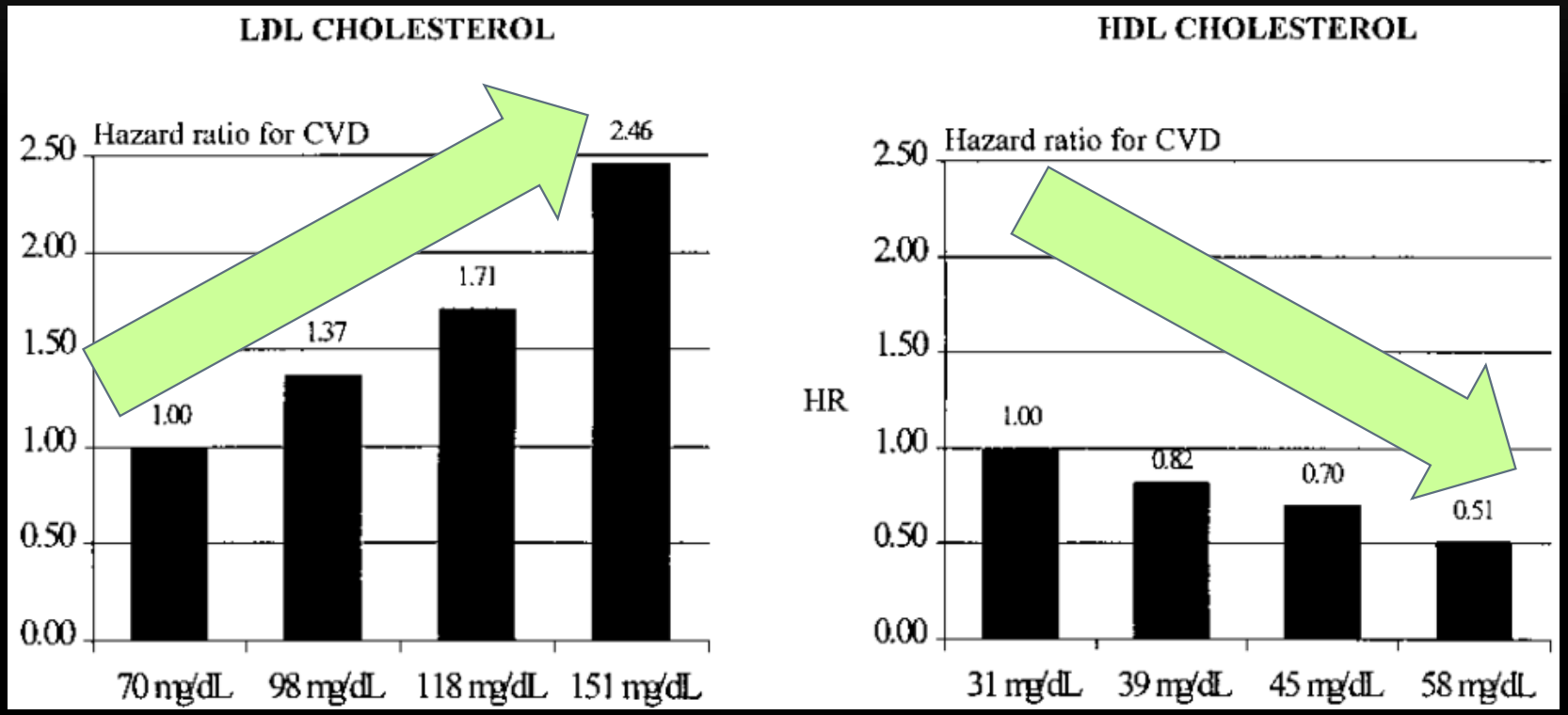
Dyslipidemia

膽固醇

- 總膽固醇 Choleterol
- 高密度膽固醇　ＨＤＬ
- 低密度膽固醇　ＬＤＬ
- 三酸甘油脂　ＴＧ

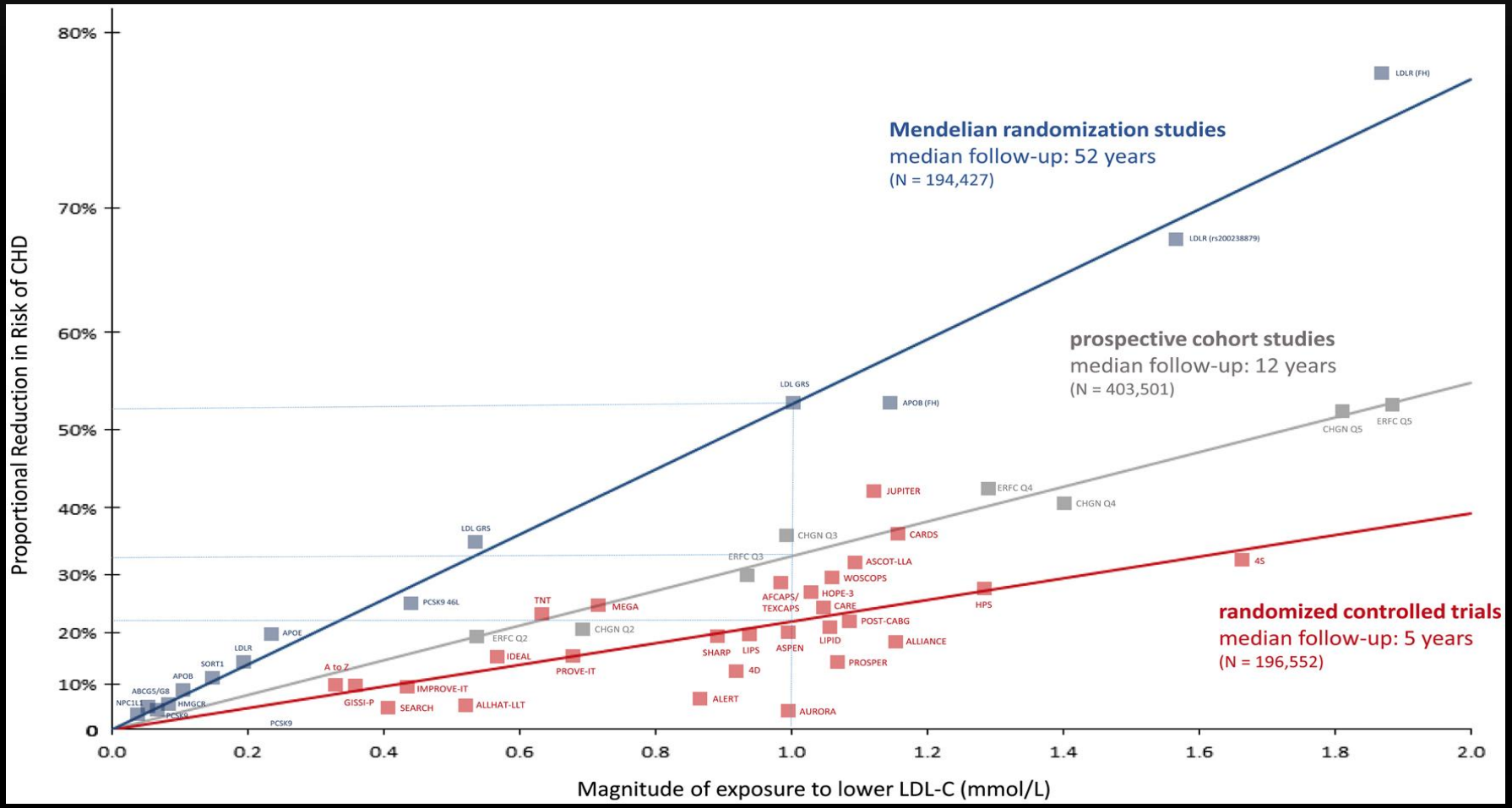


LDL & HDL



Arterioscler Thromb Vasc Biol. 2000;20:830-835

LDL Study



European Heart Journal 2017; 285:2264-2271

LDL 與 心血管風險評估 *(初級預防)*

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaborators**

- LDL↓ **~40**mmol/L
  ➔ 心血管風險↓ 25%

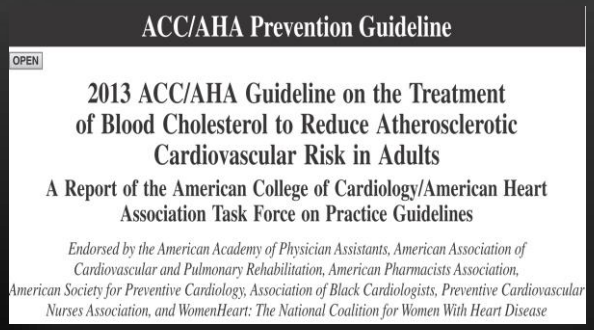
Lancet 2012; 380: 581–90

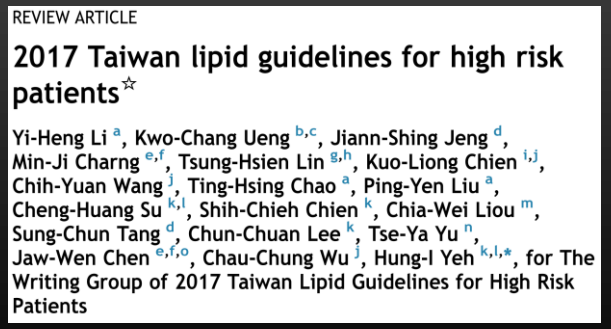
哪種血脂肪比較重要?

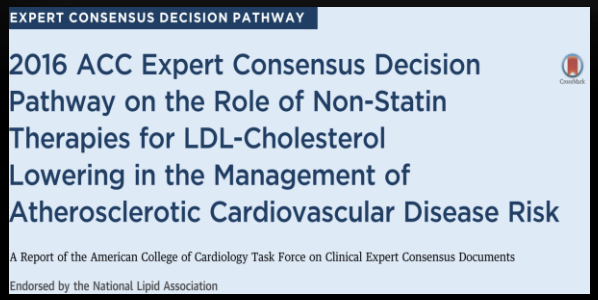
Recommendations	Class [a]	Level [b]
LDL-C has to be used as the primary lipid analysis.	I	C
It is recommended to analyse HDL-C before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
When available, apoB should be an alternative to non-HDL-C.	IIa	C
Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD (**see Box 7**).	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C
HDL-C is not recommended as a target for treatment.	III	A

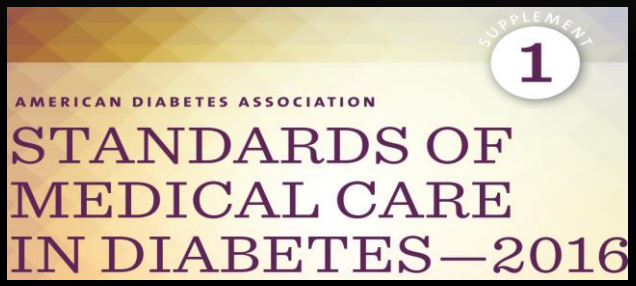
LDL
低密度
膽固醇

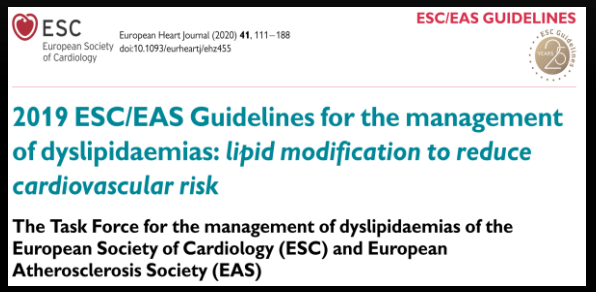
歐洲心臟學會治療指引











- 2013 Australia/New Zealand Guideline(澳洲/紐西蘭)
- 2013 AHA Guideline (美國心臟學會)
- 2016 ACC Expert consensus(Non-Statin) (美國專家會議)
- 2016 ADA Guideline (美國糖尿病學會)
- 2017 Taiwan (台灣專家會議)
- 2019 ESC Guideline (歐洲)

各國治療指引

	LDL-C 目標 (mg/dL)		
	沒有心血管疾病*	有心血管疾病	替代目標
AHA(美國) [1]	< 100	< 70	降幅30 – 40 %
ADA(美國) [2]	< 100	< 70	降幅30 – 40 %
ESC(歐洲) [3]	< 100	< 70	
JAS(日本) [4]	< 120	< 100	降幅20 – 30 %
CCS(加拿大)[5]	< 120	< 70	降幅> 50 %

1 2013 ACC/AHA Blood Cholesterol Guideline

2 Diabetes Care 2012; 35: S11–S63.

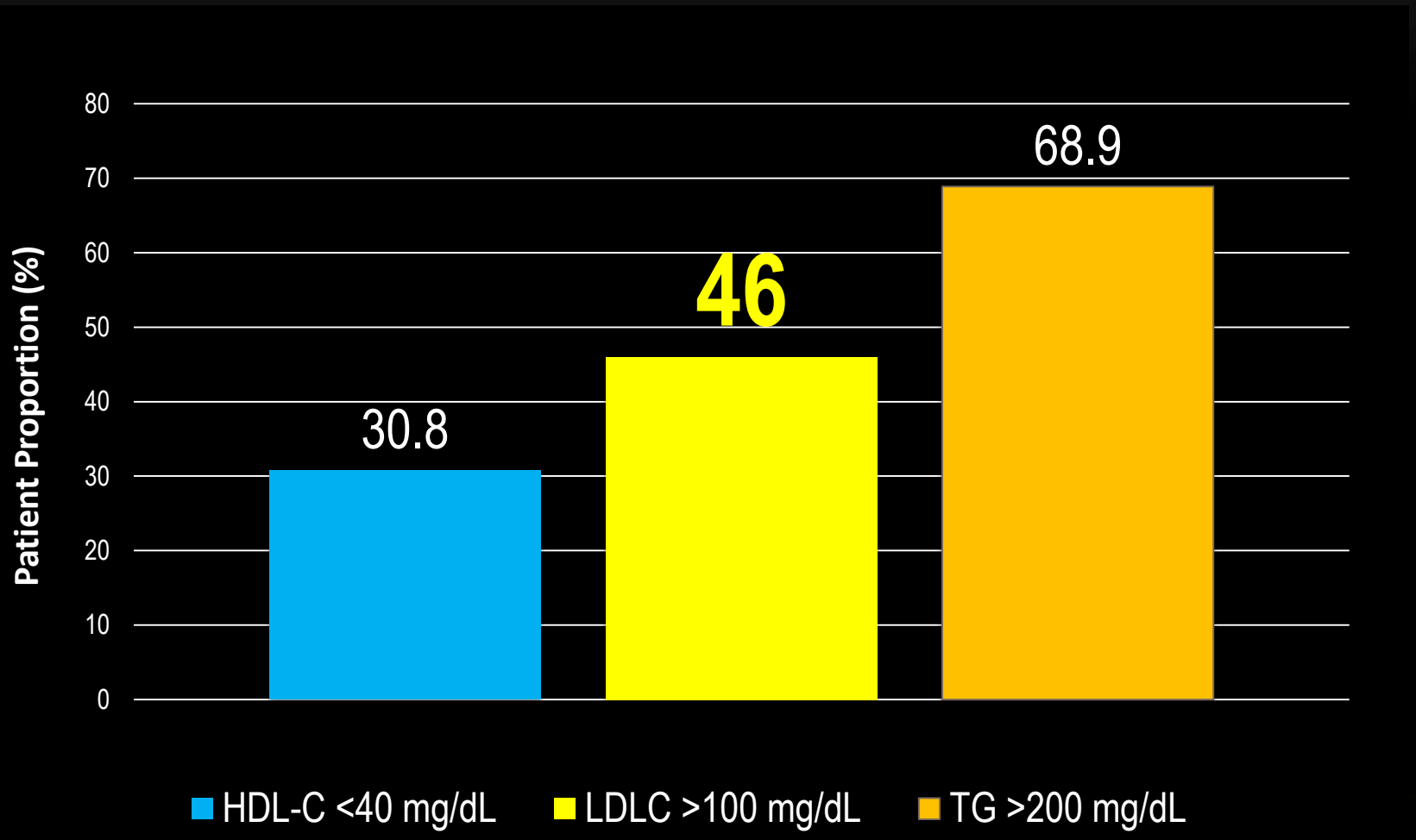
4 Eur Heart J 2011; 32: 1769– 1818

4 J Atheroscler Thromb 2007; 14: 55–158

5 Canadian Journal of Cardiology 29 (2013) 151–167 For Intermittent risk group (IR, FRS= 10-20%)

LDL control in Taiwan

(T-SPARCLE Study, CV patients)



PLoS One. 2015 Mar 10;10(3):e0116513

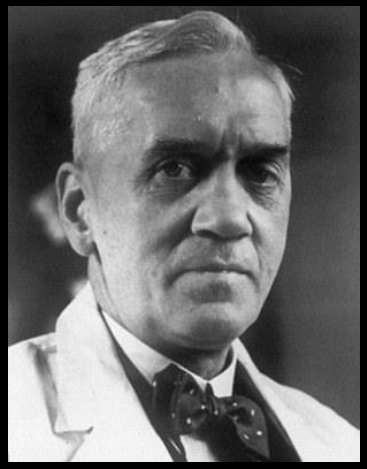
Standard of Care

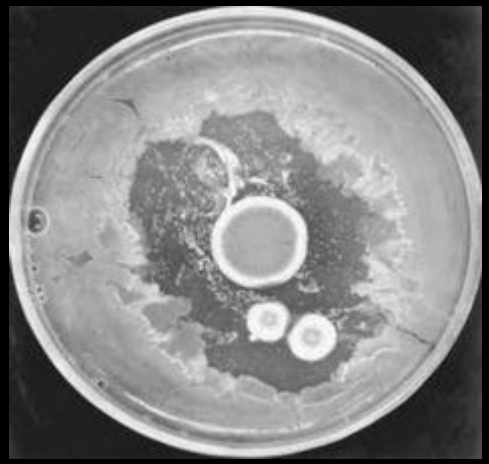
LDL

The Lower, The Better?

Mold 黴菌

Oyster Mushrooms　袖珍菇





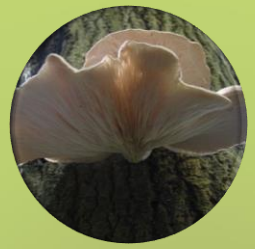
Alexander Fleming (1881~1955)
Penicillin, 1928 (47 y/o)

History of Lipid Control

1970s[1]

Dr. Endo(85 y/o)

HMG-CoA reductase



1987[2]

Lovastatin

1st US FDA Statin

1991[3]

Pravastatin

3rd Statin

Lots of Statin !

PCSK9-I

Ezetimibe

1. *J Antibiot (Tokyo). 1976 Dec; 29(12):1346-8*
2. *FDA Orange Book Detail for application N019643*
3. *Analogue-based Drug Discovery. John Wiley & Sons. p. 472(2006)*

降血脂藥物的歷史演進

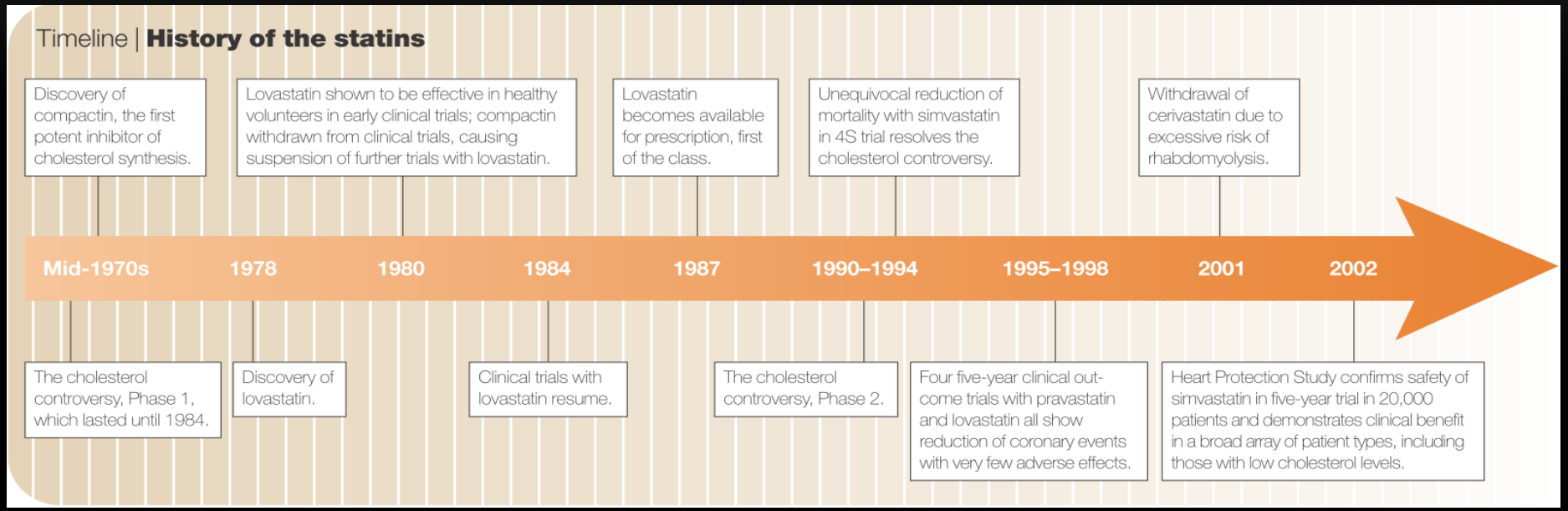


Table 1 | **Mortality by cause in 4S**

Cause of death	Simvastatin (*n* = 2,221)	Placebo (*n* = 2,223)	Risk reduction
Coronary	111	189	42% ($p<0.00001$)
Other cardiovascular	18	25	
Non-cardiovascular	46	49	
All causes	182	256	30% ($p = 0.0003$)

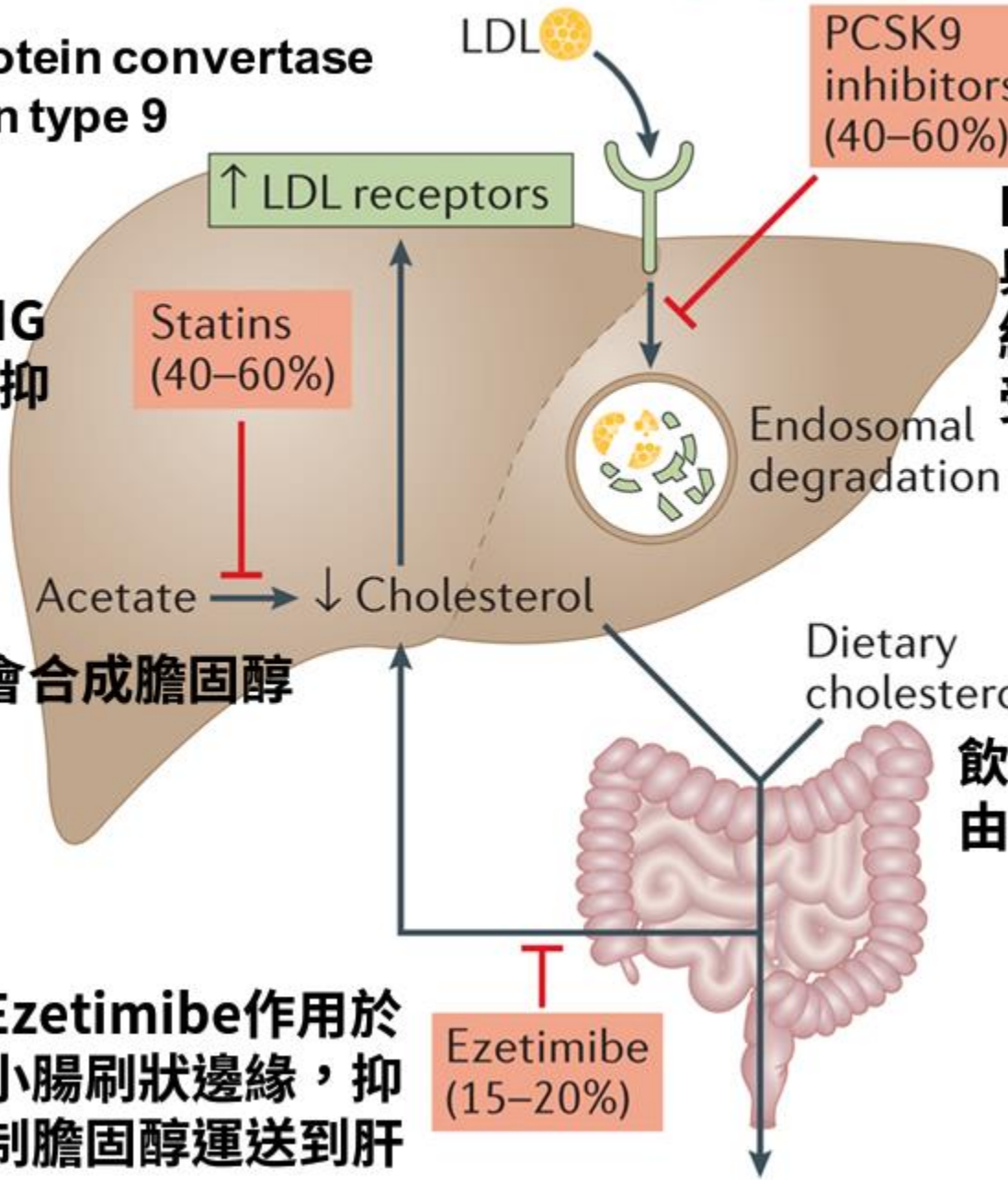
4S: Scandinavian Simvastatin Survival Study; Lancet (1994)

Nature Review, Volume 2, July, 2003

治療高血脂新藥PCSK9抑制劑

the New England Journal of Stupid

PCSK9, proprotein convertase subtilisin/kexin type 9



1

Statin抑制HMG-CoA還原酶，抑制膽固醇合成

肝臟會合成膽固醇

3

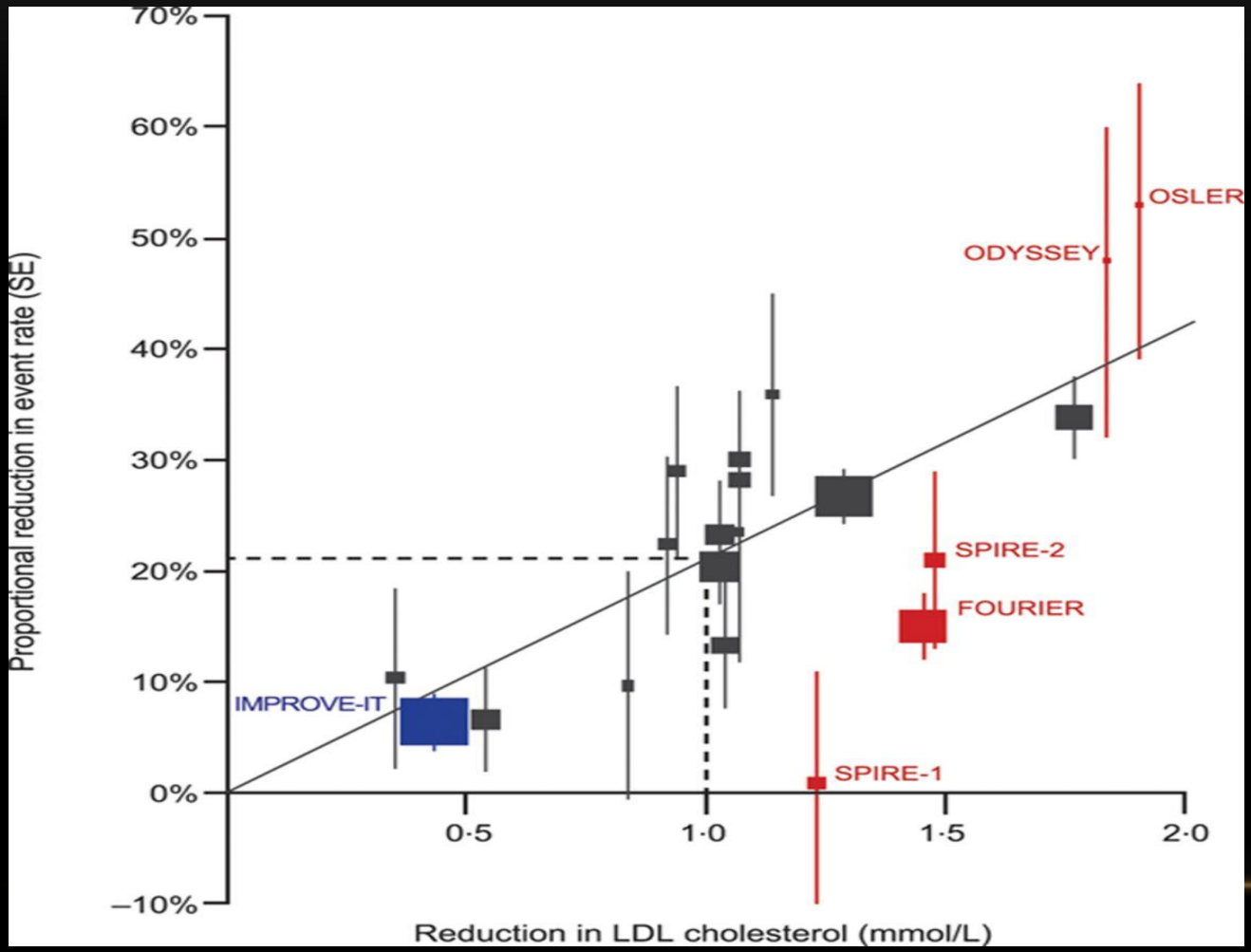
PCSK9單株抗體與PCSK9競爭性結合，減少LDL受體被分解

飲食中的膽固醇由腸胃道吸收

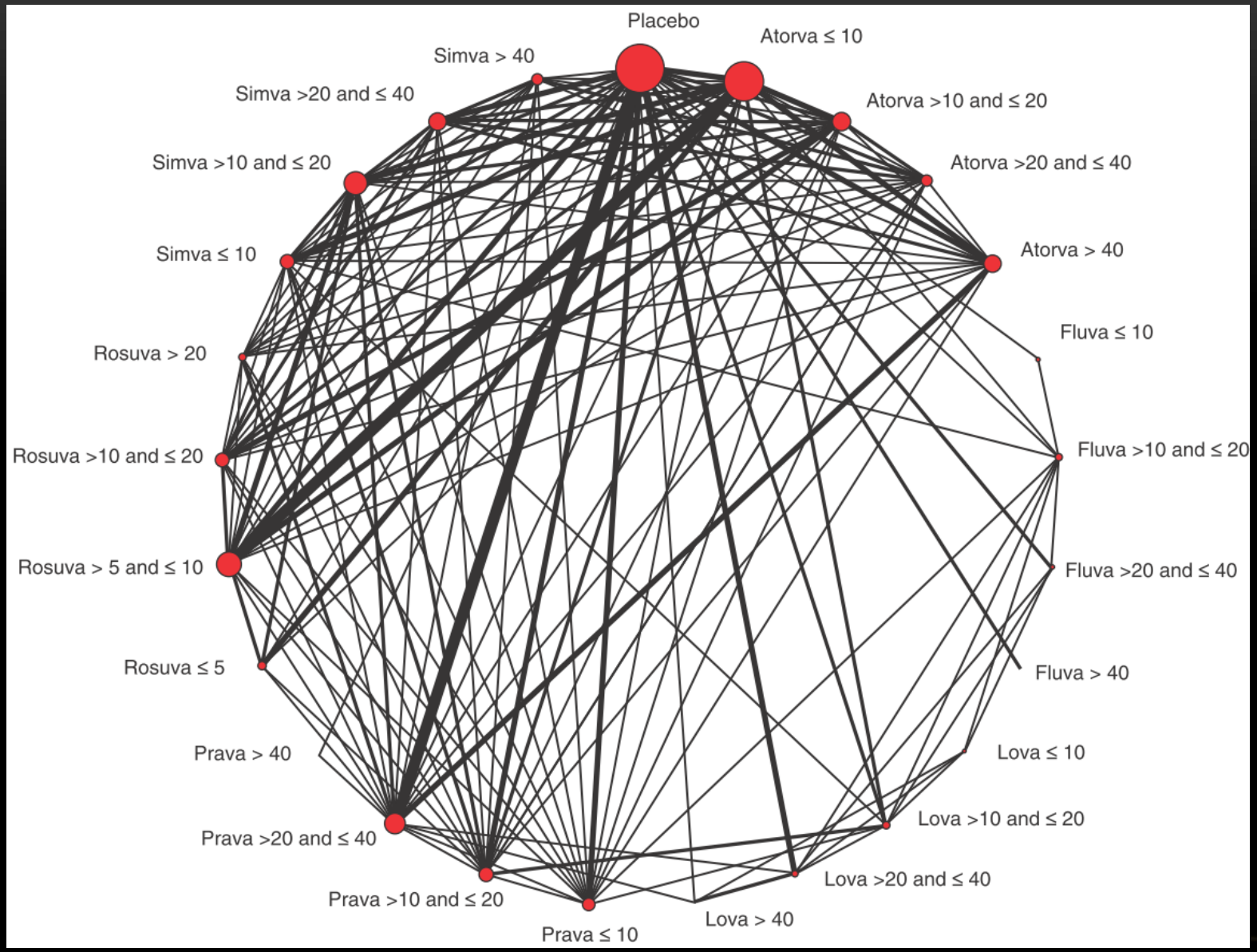
2

Ezetimibe作用於小腸刷狀邊緣，抑制膽固醇運送到肝

Lipid Control Trials



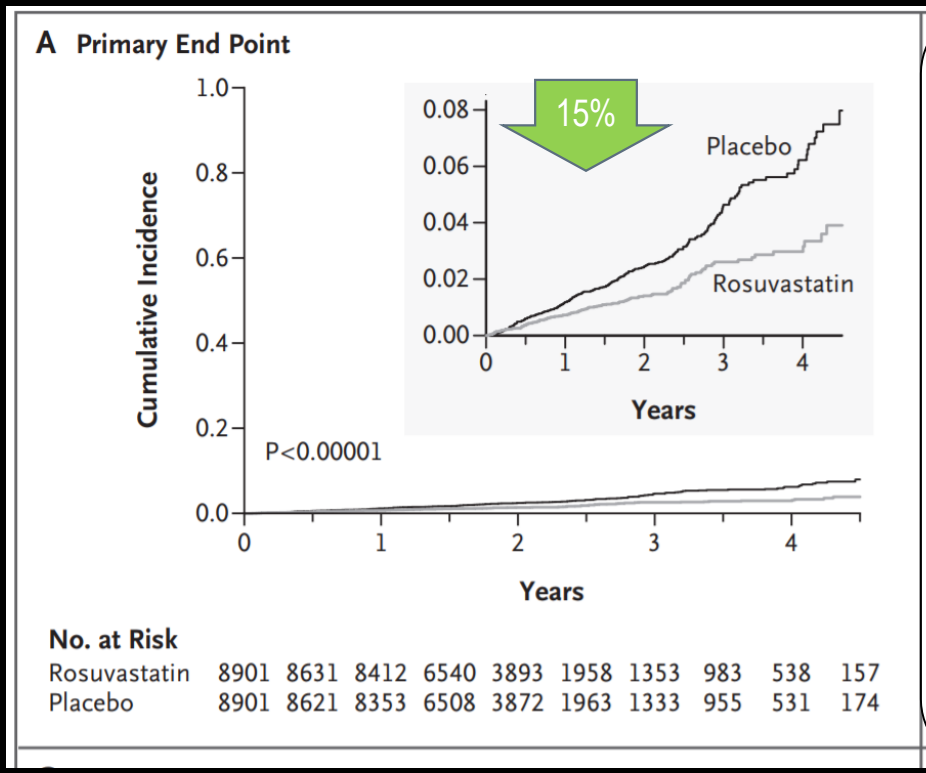
Circulation Research. 2017;120:1537-1539

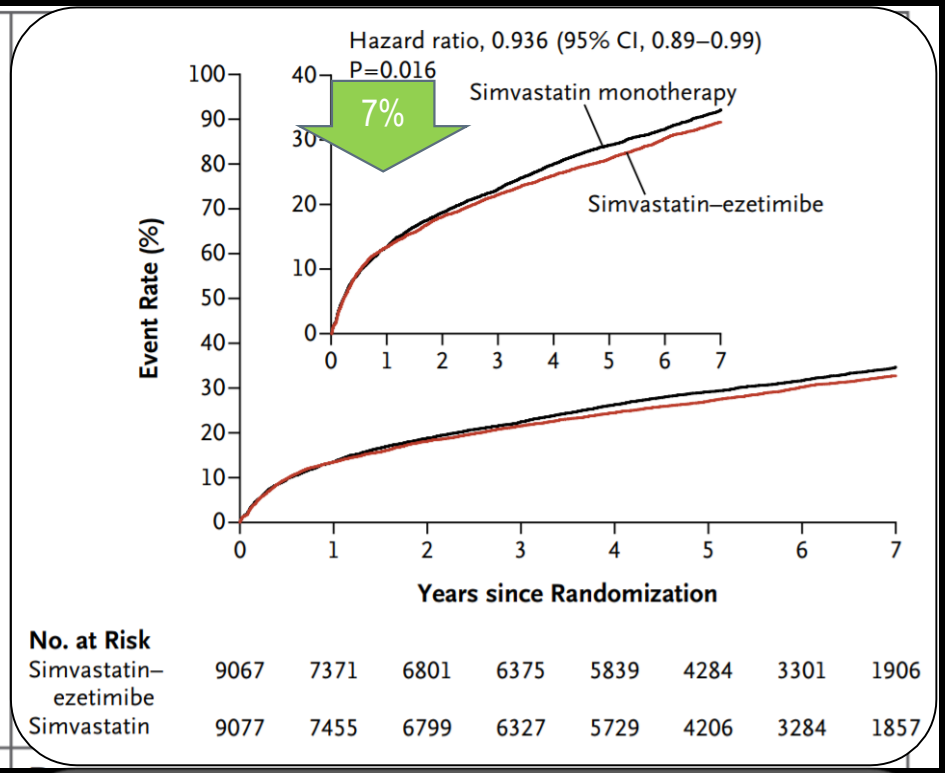


European Journal of Preventive Cardiology 2013 20: 658

Clinical Trials Review

- Statin: **JUPITOR** (Rosuvastatin), **IMPROVE-IT** (Vytorin)

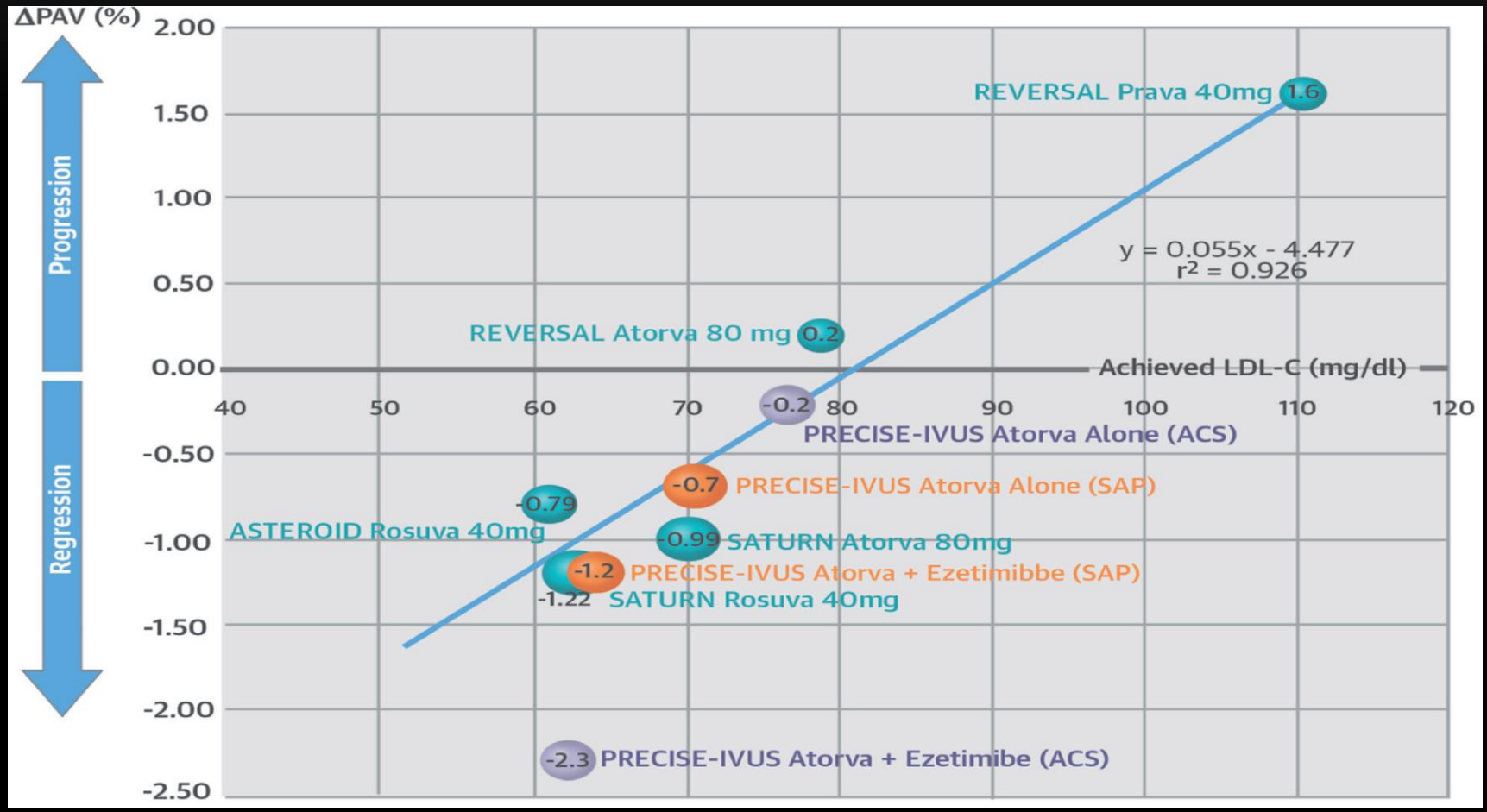




N Engl J Med 2015;372:2387-97

N Engl J Med 2008;359:2195-207

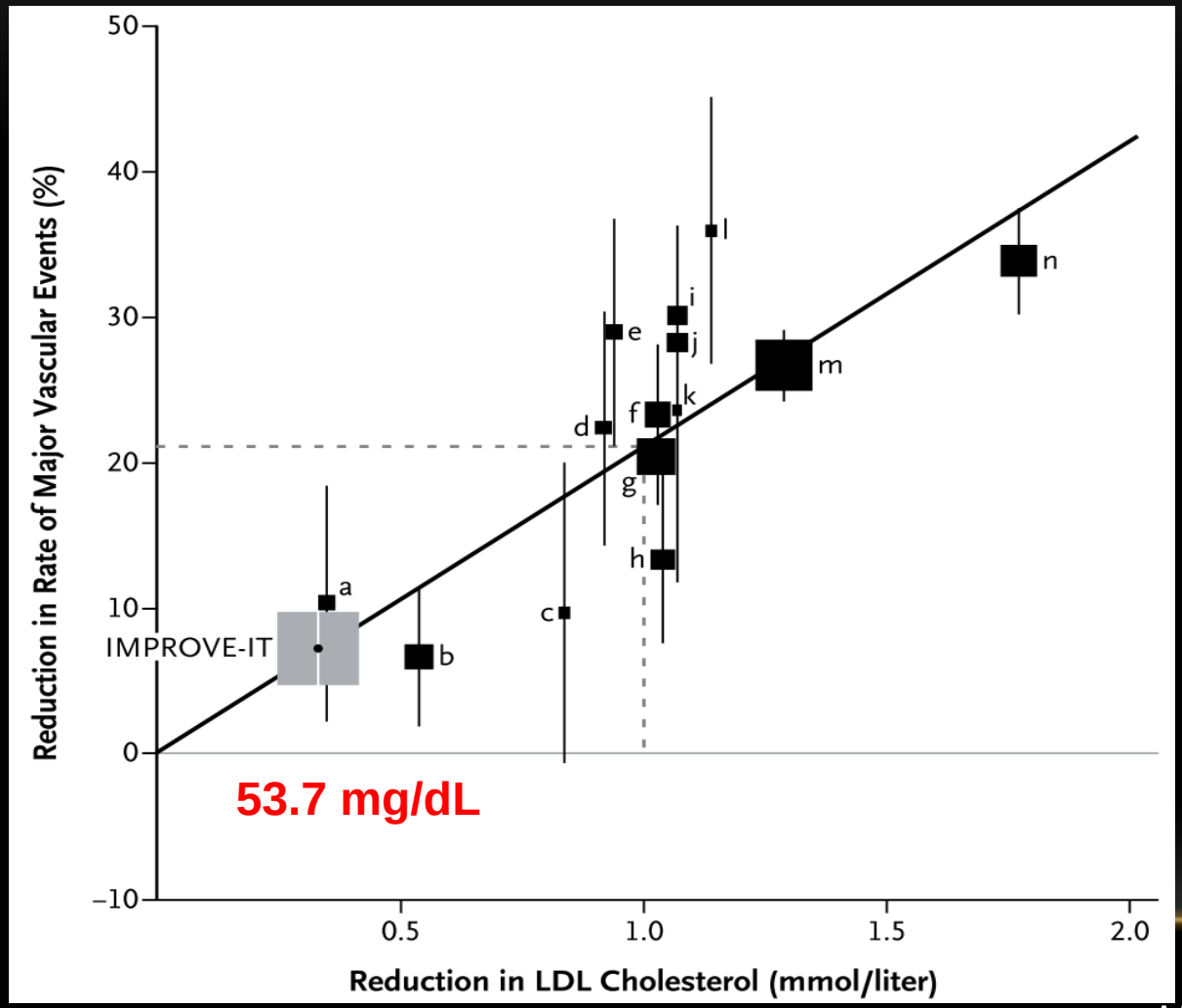
PAV & LDL



* PAV: Percent Atheroma Volume

JACC VOL. 66, NO. 5, 2015

The Lower. The Better (????)

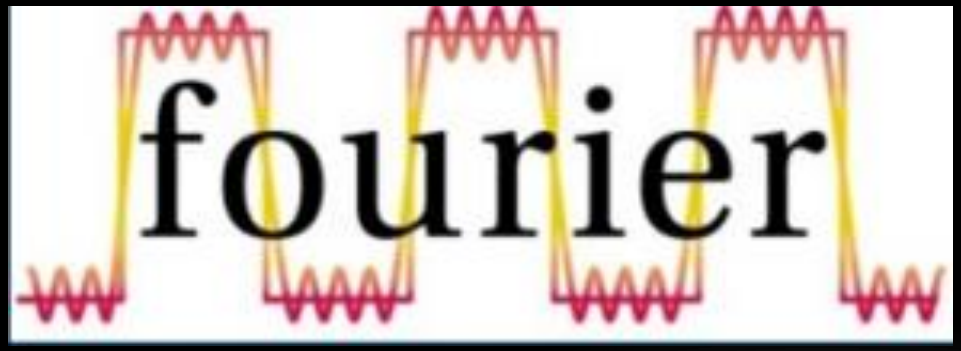


- a: GISSI Prevenzione
- b: ALLHAT-LLT trial
- c: ALERT trial
- d: LIPS trial
- e: AFCAPS/TexCAPS trial
- f: CARE trial
- g: LIPID trial
- h: PROSPER trial
- i: ASCOT-LLA trial
- j: WOSCOPS trial
- k: Post CABG trial
- l: CARDS trial
- m: HPS trial
- n: 4S trial

N Engl J Med 2015;372:2387-97

CV Outcome of PCSK-9 Inhibitor

N Engl J Med 2018;379:2097-107



N Engl J Med 2017;376:1713-22

PCSK9 Inhibitor- Evolocumab

The NEW ENGLAND JOURNAL of MEDICINE

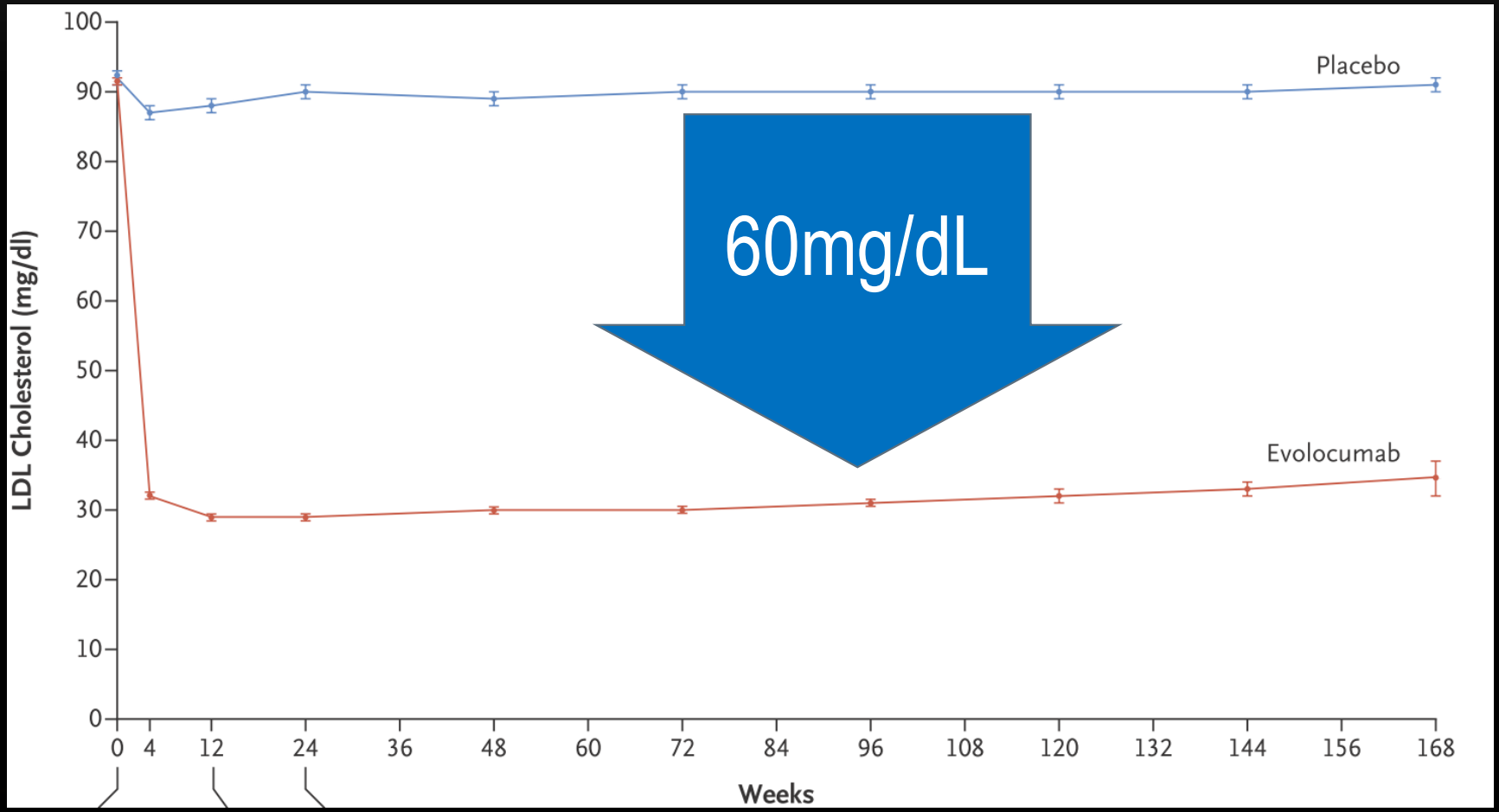
ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

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*

N Engl J Med 2017;376:1713-22

LDL Outcome



N Engl J Med 2017;376:1713-22

Outcome

Table 2. Primary and Secondary End Points.

Outcome	Evolocumab (N = 13,784)	Placebo (N = 13,780)	Hazard Ratio (95% CI)	P Value*
	no. of patients (%)			
Primary end point: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	1344 (9.8)	1563 (11.3)	0.85 (0.79–0.92)	<0.001
Key secondary end point: cardiovascular death, myocardial infarction, or stroke	816 (5.9)	1013 (7.4)	0.80 (0.73–0.88)	<0.001
Other end points				
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

N Engl J Med 2017;376:1713-22

ODYSSEY Outcome Trial

The NEW ENGLAND JOURNAL of MEDICINE

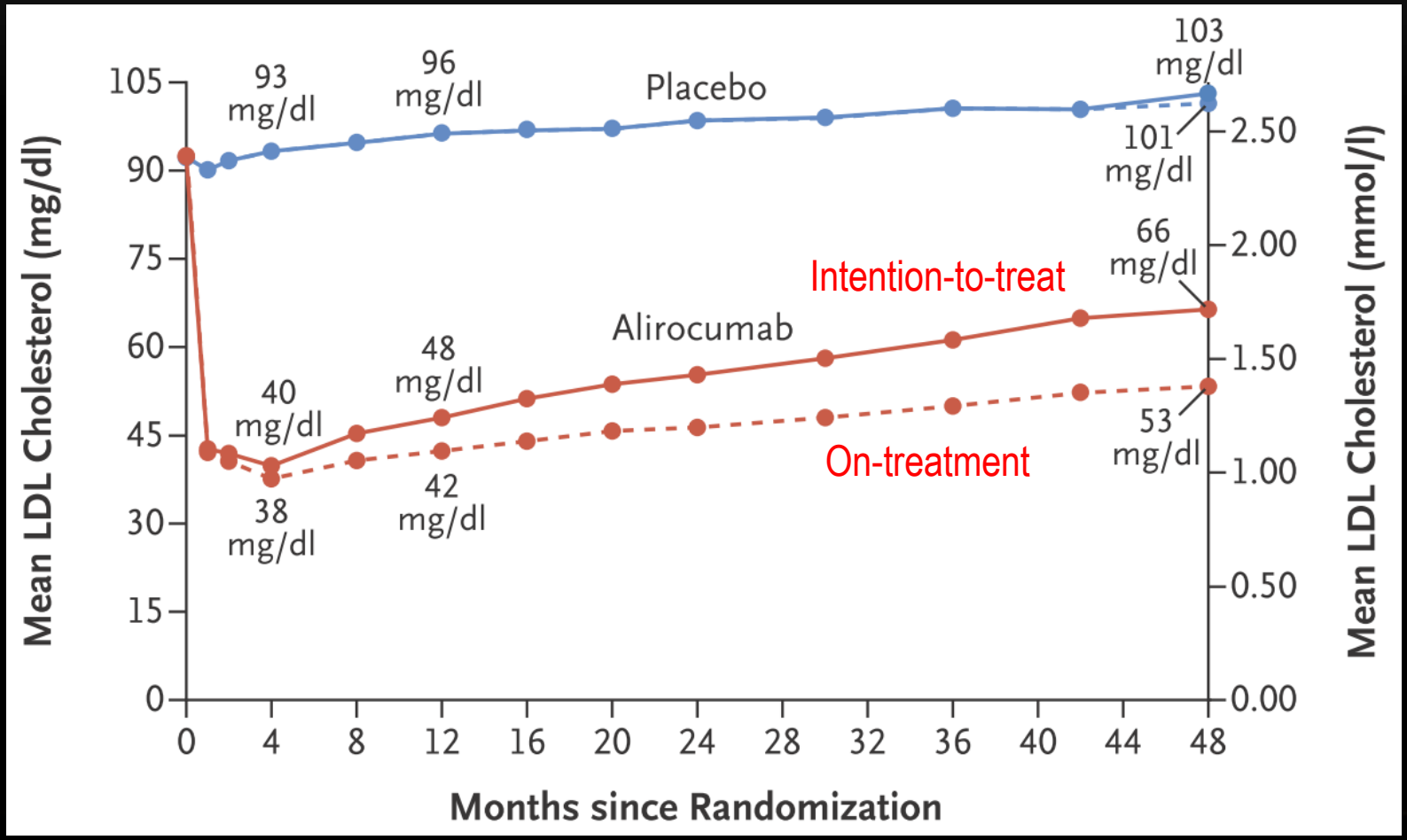
ESTABLISHED IN 1812 NOVEMBER 29, 2018 VOL. 379 NO. 22

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

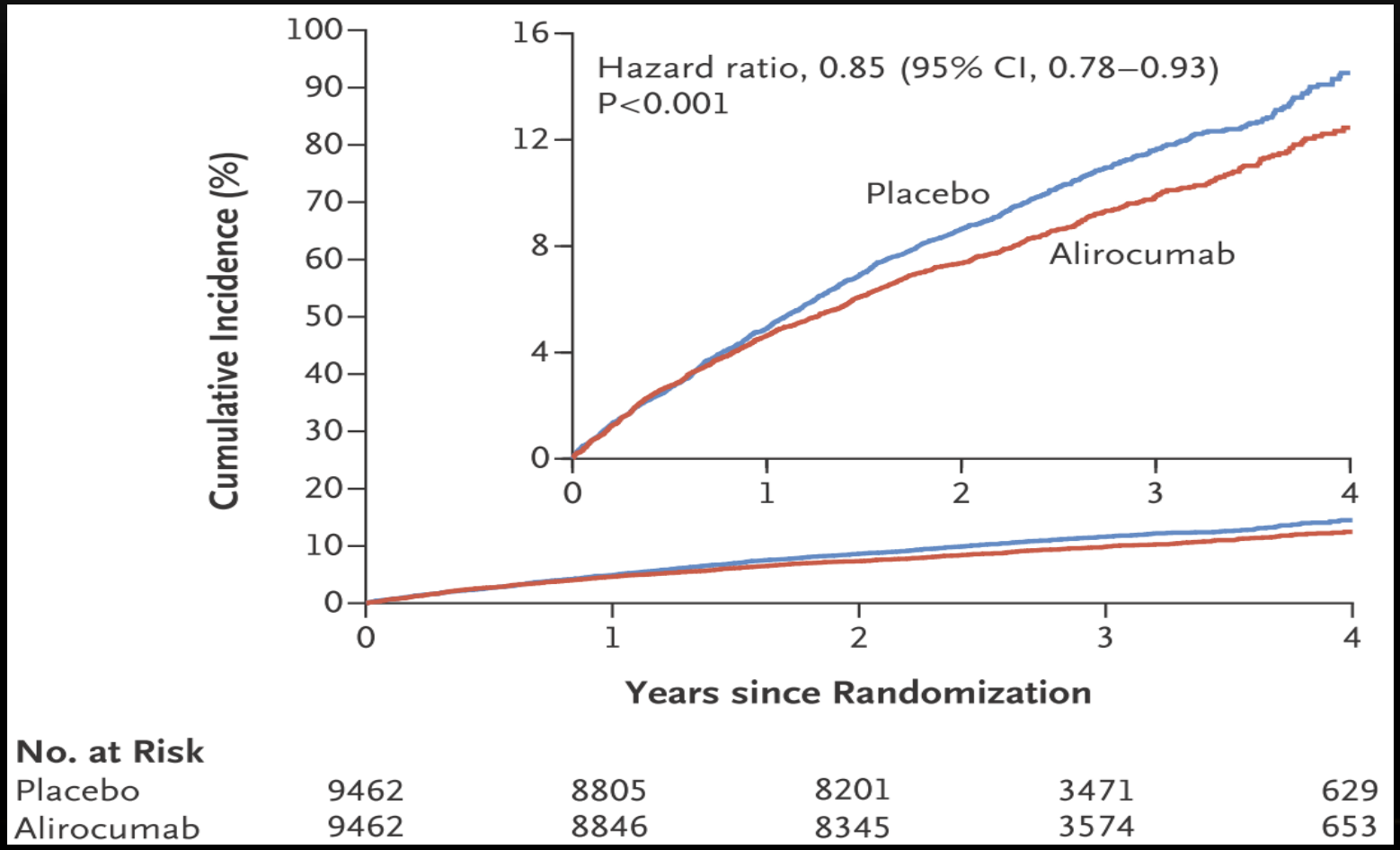
N Engl J Med 2018;379:2097-107

ODYSSEY Outcome Trial



N Engl J Med 2018;379:2097-107

ODYSSEY Outcome Trial- Outcome



N Engl J Med 2018;379:2097-107

ODYSSEY Outcome Trial- Outcome

Table 2. Composite Primary End Point and Secondary End Points (Intention-to-Treat Population).

End Point	Alirocumab (N=9462)	Placebo (N=9462)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary end point: composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization	903 (9.5)	1052 (11.1)	0.85 (0.78–0.93)	<0.001
Major secondary end points, in order of hierarchical testing				
Any coronary heart disease event*	1199 (12.7)	1349 (14.3)	0.88 (0.81–0.95)	0.001
Major coronary heart disease event†	793 (8.4)	899 (9.5)	0.88 (0.80–0.96)	0.006
Any cardiovascular event‡	1301 (13.7)	1474 (15.6)	0.87 (0.81–0.94)	<0.001
Composite of death from any cause, nonfatal myocardial infarction, or nonfatal ischemic stroke§	973 (10.3)	1126 (11.9)	0.86 (0.79–0.93)	<0.001
Death from coronary heart disease	205 (2.2)	222 (2.3)	0.92 (0.76–1.11)	0.38¶
Death from cardiovascular causes	240 (2.5)	271 (2.9)	0.88 (0.74–1.05)	
Death from any cause	334 (3.5)	392 (4.1)	0.85 (0.73–0.98)	

N Engl J Med 2018;379:2097-107

Statin? Others?

LDL control in Stable CAD/ACS
(Asia-Pacific)

Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II

Kian-Keong Poh[1,2], Baishali Ambegaonkar[3], Carl A Baxter[4], Philippe Brudi[3], Wacin Buddhari[5], Fu-Tien Chiang[6], Martin Horack[7], Yangsoo Jang[8], Brett Johnson[9], Dominik Lautsch[3], JPS Sawhney[10], Ami Vyas[11,12], Bryan P Yan[13] and Anselm K Gitt[7,14]

Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963

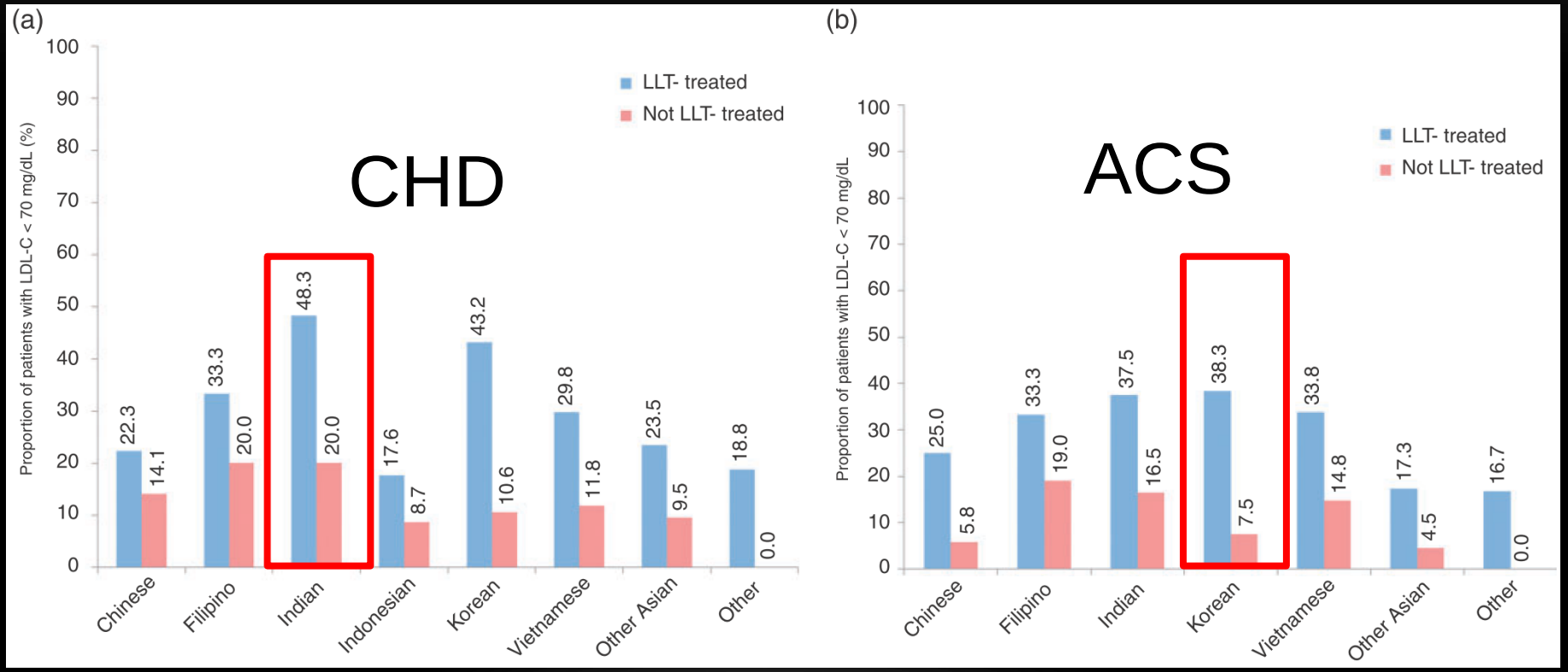
Dyslipidemia International Study
- DYSIS II -

- Observational study
  - Patients with CHD or ACS
- 2013/07 – 2014/10
- Asia-Pacific countries

- Total 4592; CHD=2794, ACS=1798

Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963

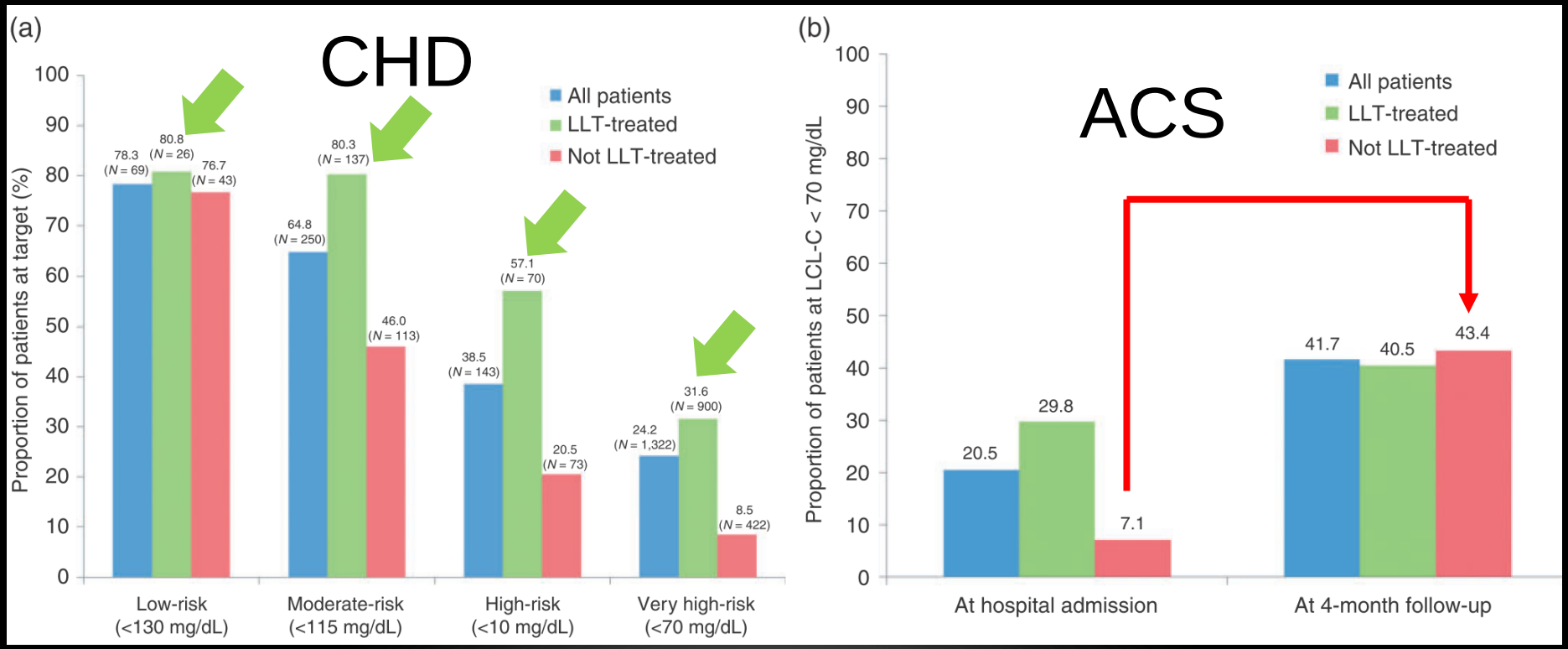
DYSIS II Study
(LDL<70, baseline)



Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963

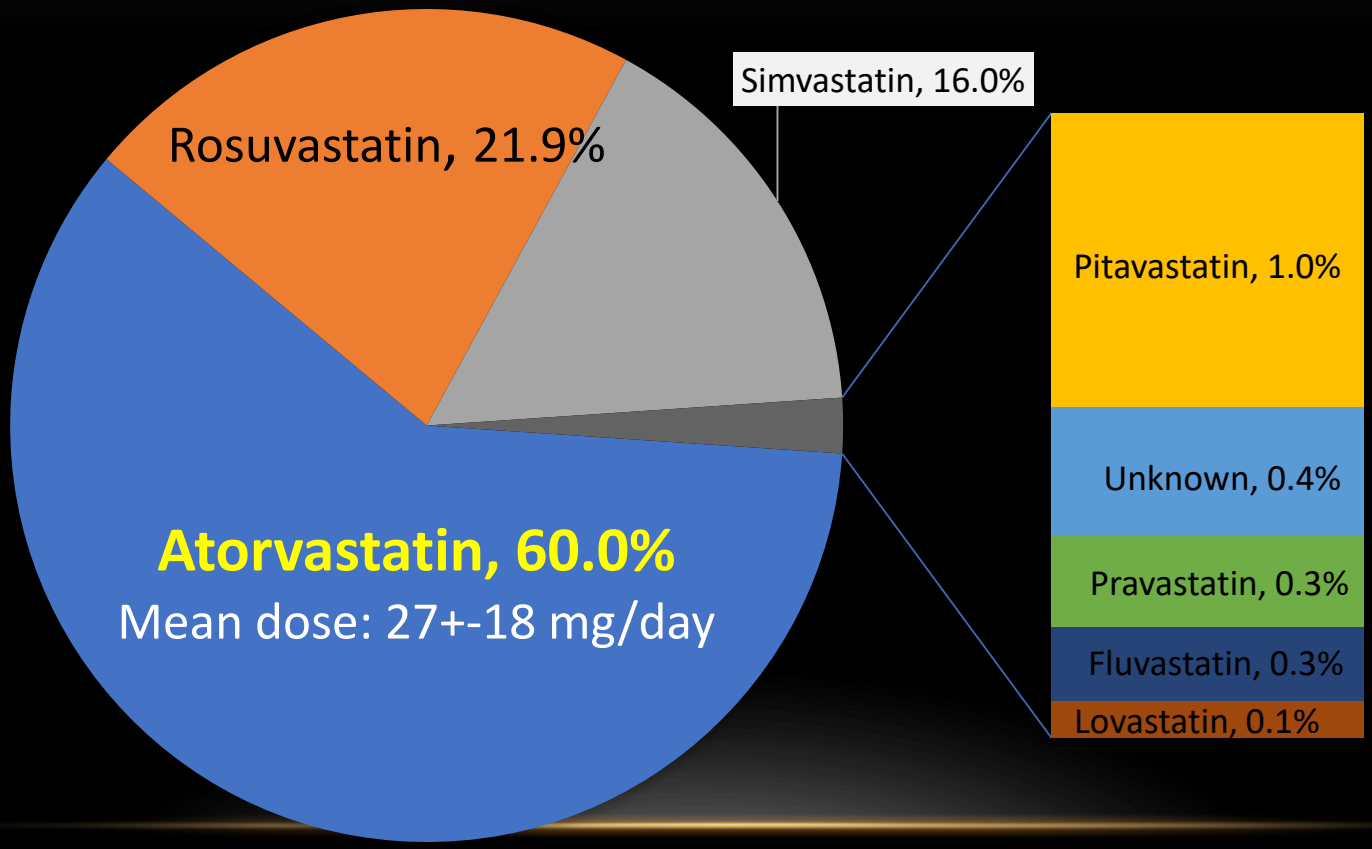
LDL control in Stable CAD/ACS (Asia-Pacific)

Proportion of P't at Target LDL



Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963

LDL Control in CHD
(Asia-Pacific)



Eur J Prev Cardiol. 2018 Dec;25(18):1950-1963

Statin in Taiwan

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

Wen-Jone Chen MD, PhD[1] | Yao-Chun Wen MS[2] | Kathleen M. Fox PhD[3] | Li-Jiuan Shen PhD[4,5,6] | Lian-Yu Lin MD, PhD[1] | Yi Qian PhD[7] | Zhongyun Zhao PhD[7] | Pratik P. Rane PhD[7] | Fei-Yuan Hsiao PhD[4,5,6]

J Eval Clin Pract. 2019 Oct 23

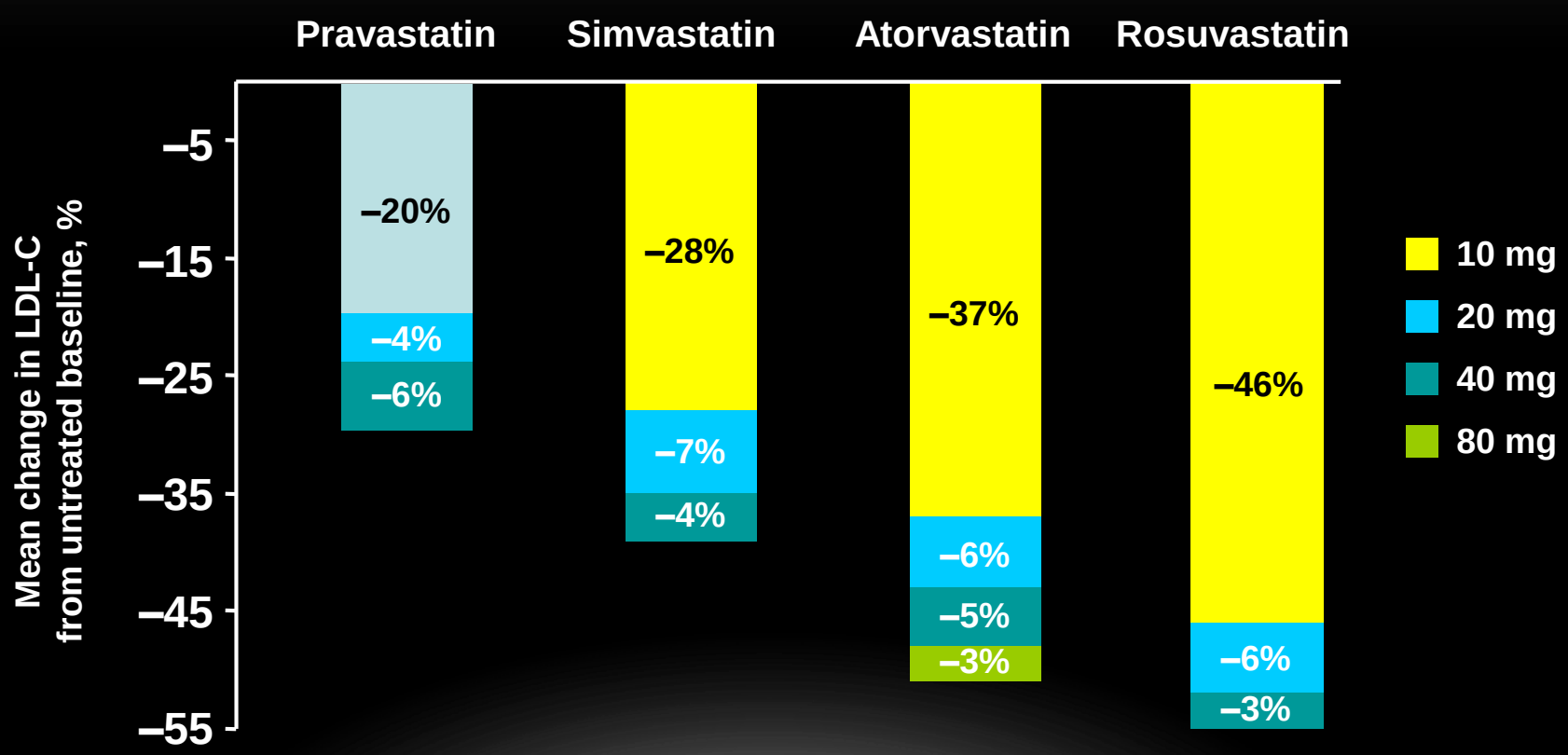
Statin in Taiwan

- Retrospective cohort study
- Duration: 2005-2013; NHIRD

	全部 (n=82608)	次分析	
		ASCVD患者 (n=11092)	DM患者 (n=31100)
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%

J Eval Clin Pract. 2019 Oct 23

Rule of “6”



Am J Cardiol. 2003;92:152–160

Ezetimibe Role

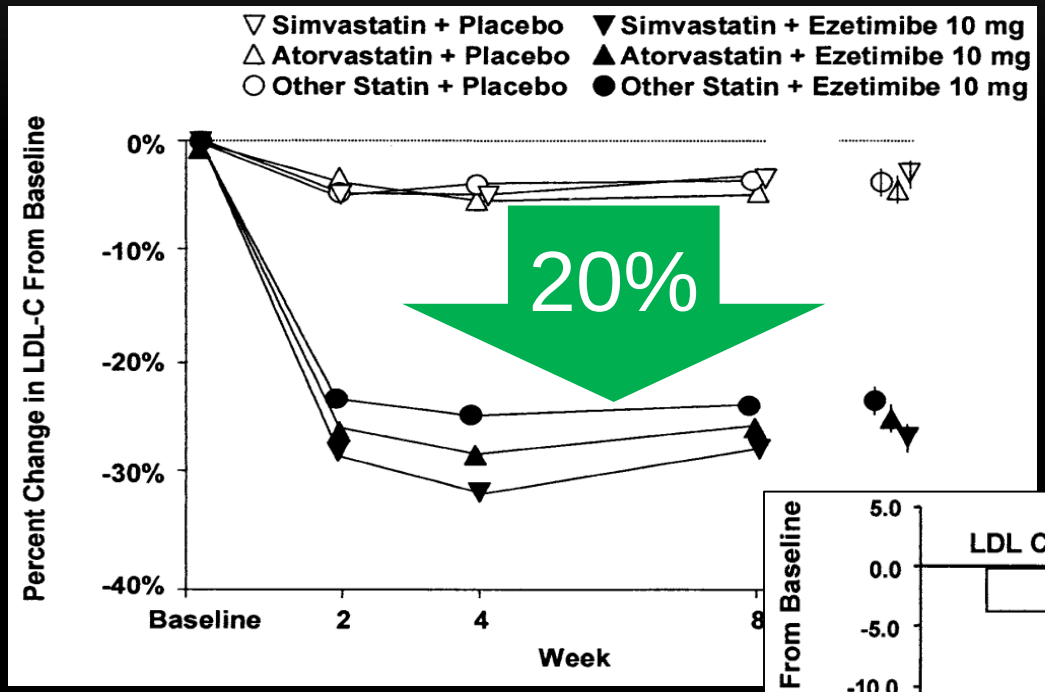
Efficacy and Safety of *Ezetimibe* Added to Ongoing Statin Therapy for Treatment of Patients With Primary Hypercholesterolemia

Claude Gagné, MD, Harold E. Bays, MD, Stuart R. Weiss, MD, Pedro Mata, MD, Katherine Quinto, BSN, RN, Michael Melino, PhD, Meehyung Cho, PhD, Thomas A. Musliner, MD, and Barry Gumbiner, MD, for the Ezetimibe Study Group*

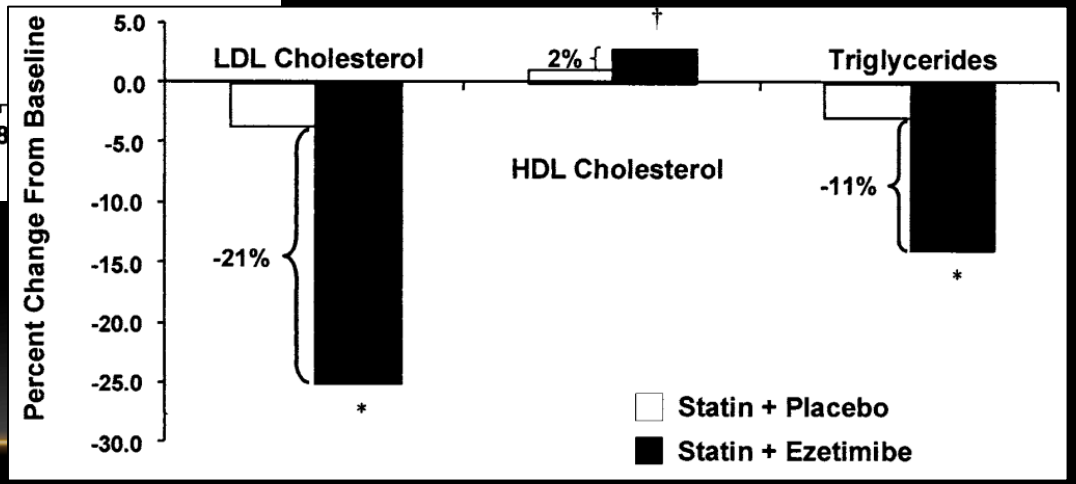
- Statin + Placebo & Statin + Ezetimibe

Am J Cardiol 2002;90:1084–1091

Ezetimibe Role

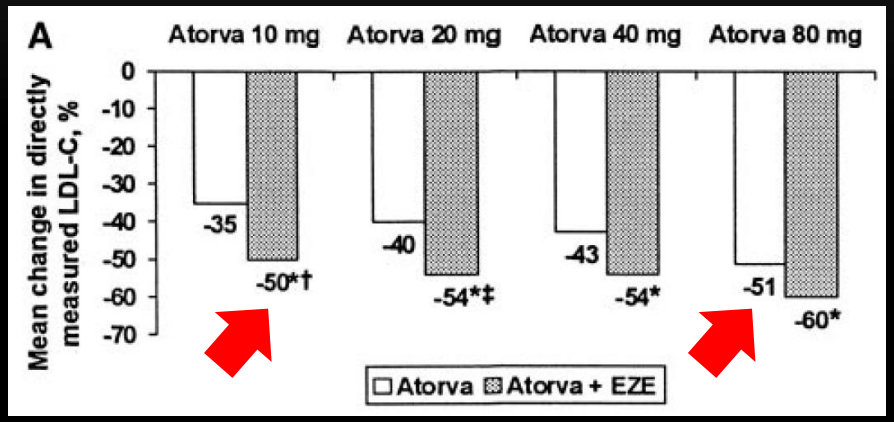


- n=769
- ~95% complete, each arm (no difference)

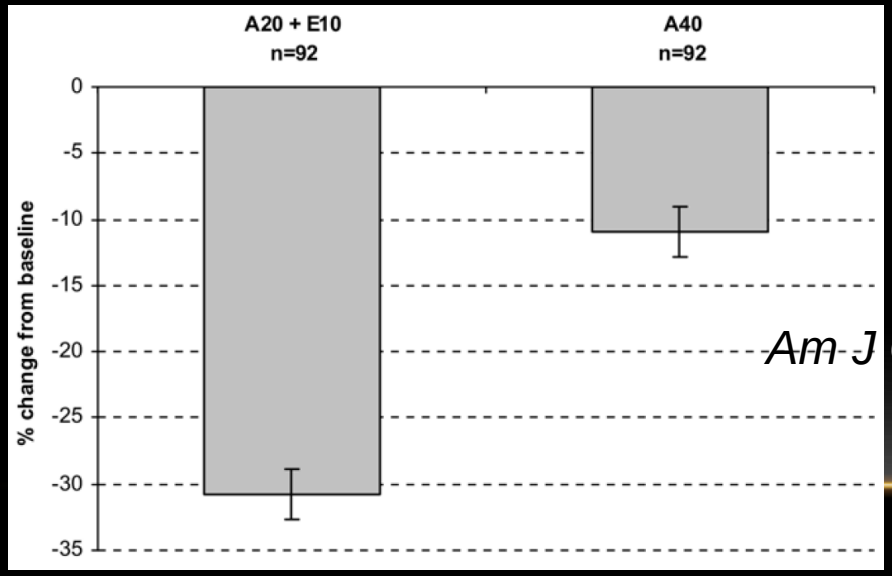


Am J Cardiol 2002;90:1084–1091

Statin + Ezetimibe

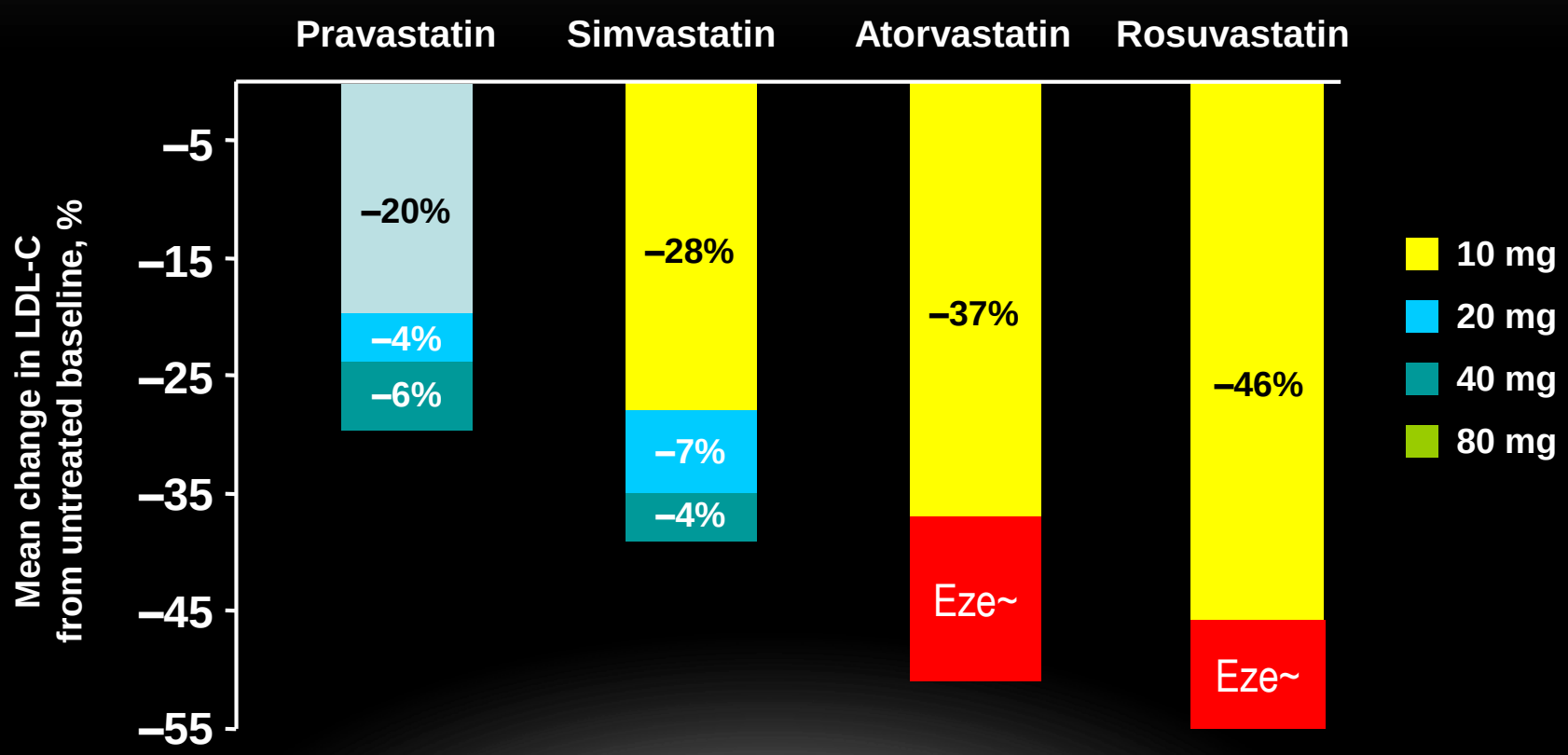


Circulation. 2003;107:2409–2415



Am J Cardiol. 2008 Dec 1;102(11):1489-94

Rule of “6”



Am J Cardiol. 2003;92:152–160

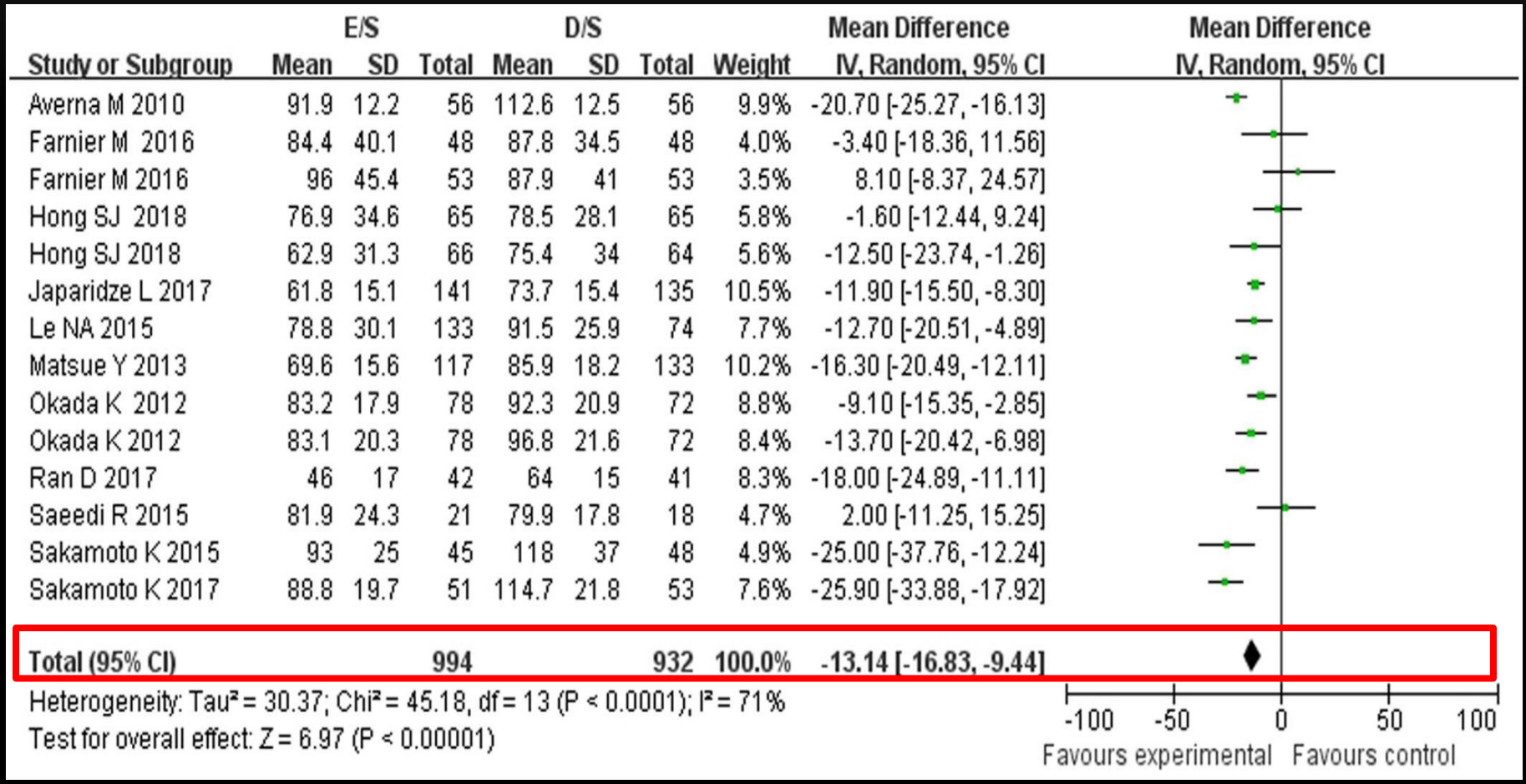
Statin + Ezetimibe & Statin*2

Study	Year	First Anthor	Country	Male	Age	Patients(n)		Therapy		follow-up	*p* value
				(%)	(Yrs)	E/S	D/S	EZE + Statin	Double Statin		
1	2018	Hong SJ	Korea	63/70	63/63	65	65	EZE 10 mg + ROS 5 mg	ROS 10 mg	8 week	< 0.001
				59/62	62/64	66	64	EZE 10 mg + ROS 10 mg	ROS 20 mg	8 week	< 0.001
2	2017	Ran D	China	76/73	60/60	42	41	EZE 10 mg + ROS 10 mg	ROS 20 mg	12 week	< 0.001
3	2017	Sakamoto K	Japan	NR	NR	51	53	EZE 10 mg + ATO 10 mg/PIT 1 mg	ATO 20 mg/PIT 2 mg	52 week	0.0002
4	2017	Japaridze L	Georgia	54/53	62/62	141	135	EZE 10 mg + ATO 20 mg/40 mg	ATO 40 mg/80 mg	16 week	< 0.001
5	2016	Farnier M	France	54/69	60/61	48	48	EZE 10 mg + ROS 10 mg	ROS 20 mg	12 week	NR
				59/72	63/60	53	53	EZE 10 mg + ROS 20 mg	ROS 40 mg	12 week	NR
6	2015	Sakamoto K	Japan	57/59	63/62	45	48	EZE 10 mg + ATO 10 mg/PIT 1 mg	ATO 20 mg/PIT 2 mg	12 week	< 0.001
7	2015	Saeedi R	Canada	95/85	56/57	21	18	EZE 10 mg + ROS 10 mg	ROS 20 mg	12 week	0.37
8	2015	Le NA	American	NR	64/64	133	74	EZE 10 mg + SIM 20 mg	SIM 40 mg	12 week	<0.01
9	2013	Matsue Y	Japan	72/75	69/70	117	133	EZE 10 mg + ATO 10 mg	ATO 20 mg	12 week	< 0.001
10	2012	Okada K	Japan	73/74	65/65	78	72	EZE 10 mg + ATO 10 mg/ROS 2.5 mg	ATO 20 mg/ROS 5 mg	12 week	<0.01
				73/74	65/65	78	72	EZE 10 mg + ATO 10 mg/ROS 2.5 mg	ATO 20 mg/ROS 5 mg	52 week	<0.01
11	2010	Averna M	Italy	54/57	61/62	56	56	EZE 10 mg + SIM 20 mg	SIM 40 mg	6 week	< 0.001

Data reported as Ezetimibe+Statin/Double-dose Statin(E/S, D/S)
Abbreviations: *EZE* Ezetimibe, *ROS* Rosuvastatin, *SIM* Simvastatin, *ATO* Atorvastatin, *PIT* Pitavastatin, *NR* Not reported

Lipids in Health and Disease (2020) 19:1

Change in LDL



Lipids in Health and Disease (2020) 19:1

台灣血脂健保給付規範更新(108/02/01)

	起始藥物治療血脂值	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	
2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	

- 心血管疾病定義：

(一)冠狀動脈粥狀硬化患者包含：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)

(二)缺血型腦血管疾病患者包含：1.腦梗塞。2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）

- 危險因子定義：1.高血壓2.男性≧45歲，女性≧55歲或停經者3.有早發性冠心病家族史(男性≦55歲，女性≦65歲)4.HDL-C<40mg/dL5.吸菸(因吸菸而符合起步治療準則之個案，若未戒菸而要求藥物治療，應以自費治療)。

Take Home Message

- DM, CVD(CAD, CVA) and PAD are high risk patients
- LDL is a important nightmare in Atherosclerosis and mortality
- Control LDL is a issue for CV events prevention
- Statin is a first-line medication for lipid control

Take Home Message

- “The lower, the better” is only for Statin-based therapy, not for LDL
- Statin always discontinue in real-world data
  - Statin intolerance is a major problem
- Lower Statin dosage with Ezetimibe is a alternative therapy, compare with high Statin Tx

~ Thanks for Your Attention ~

Des Glaneuses, 1857 *Jean-François Mille*