Intensifying Statin Therapy on Diabetic Dyslipidemia to Maximize Cardiovascular Risk Reduction

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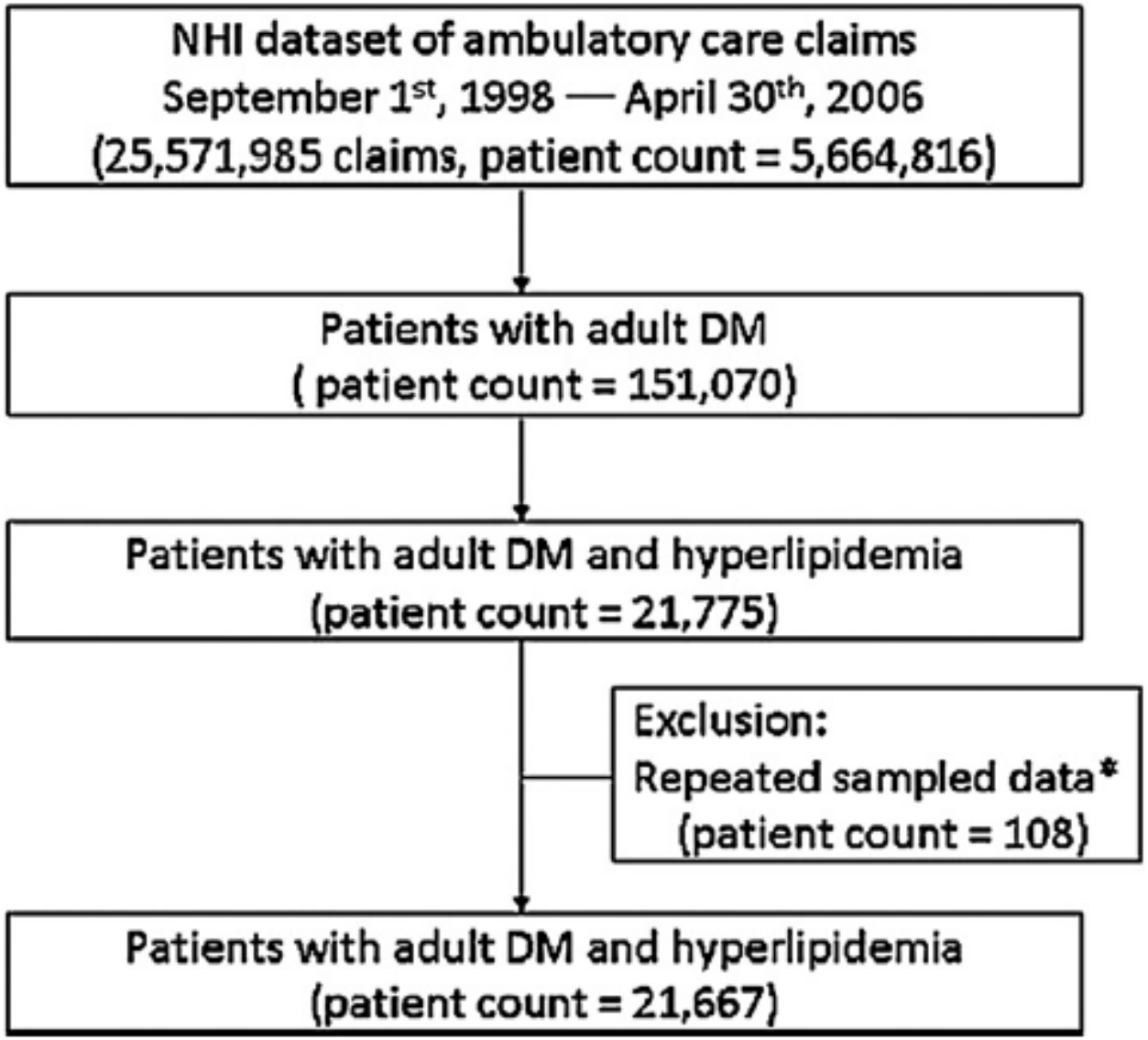
Table 3 Prevalence of hyperlipidemia in Taiwan based on various populations.

Author, year	Study period	Study design and participants	Definition	Men (%)	Women (%)
Pan and Chiang, 1995[9]	1991–1993	Ju-Dung, $n = 77,789$, age ≥35 y	Total cholesterol ≥ 240 mg/dL	9–13	7–18
	1991–1993	Pu-Tzu, $n = 45,018$, age ≥35 y	Total cholesterol ≥ 240 mg/dL	7–18	5–17
	1990	National survey, age 35–64 y	Triglycerides ≥ 200 mg/dL	12.0	7.0
Chang et al, 2002[10]	2002	National survey, $n = 5643$, age ≥45 y	Total cholesterol ≥ 240 mg/dL or on medication	12.6	24.4
			Triglycerides ≥ 200 mg/dL or on medication	12.3	11.9
			LDL-C ≥160 mg/dL	14.8	17.2
			HDL-C < 35 mg/dL	14.4	9.5
Chien et al, 2005[11]	1990–1991	Chin-Shan, $n = 3605$, age ≥35 y	Total cholesterol ≥ 240 mg/dL	14.1	19.8
			Triglycerides ≥ 200 mg/dL	14.4	12.0
			HDL-C < 40 mg/dL	36.5	27.0
			LDL-C ≥ 160 mg/dL	24.7	31.5
Pan et al, 2011[3]	1993–1996	National survey, age ≥19 y	Total cholesterol ≥ 240 mg/dL	10.2	11.2
	2005–2008		Total cholesterol ≥ 240 mg/dL	12.5	10.0
	1993–1996		Triglycerides ≥ 200 mg/dL	13.4	6.1
	2005–2008		Triglycerides ≥ 200 mg/dL	20.8	7.9

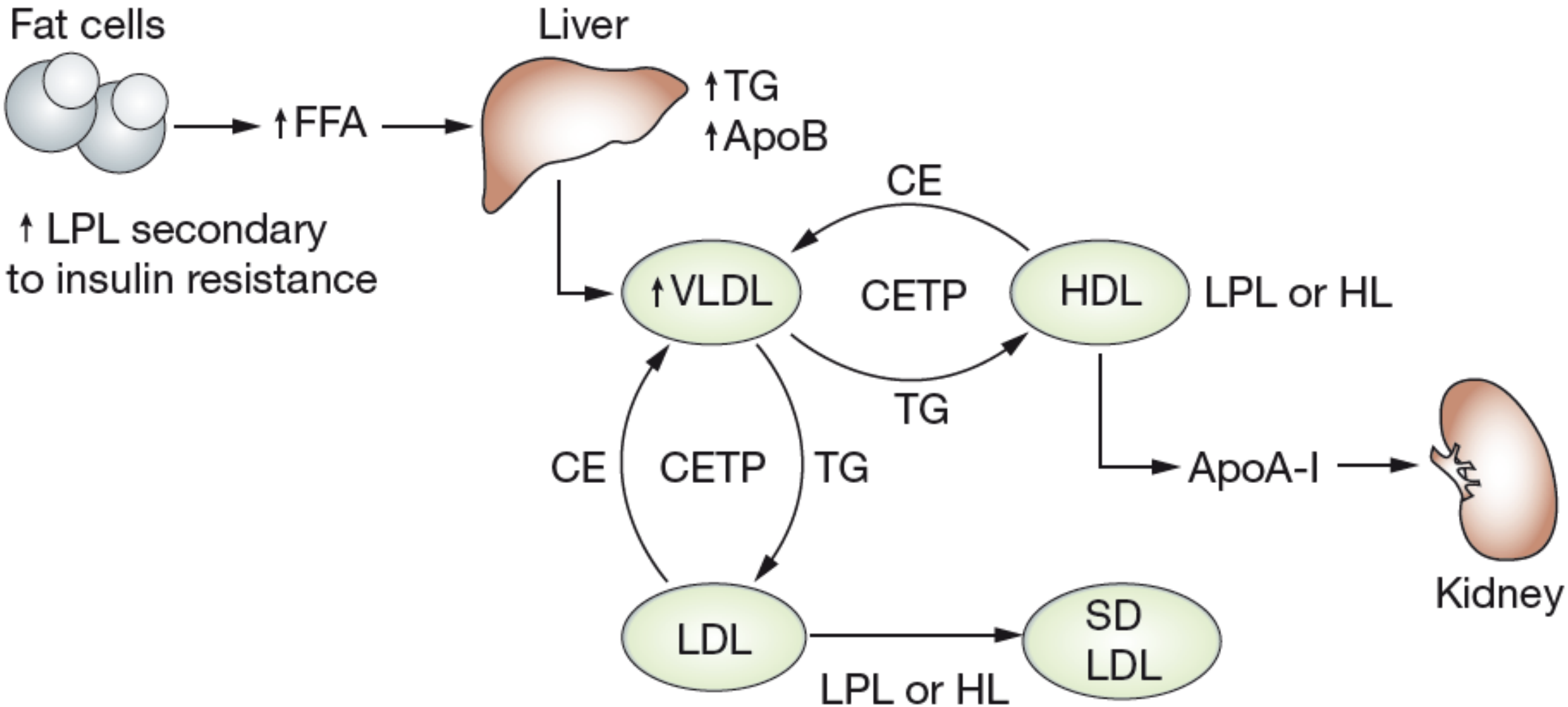
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Li, et al. *J Formos Med Assoc.* 2017; **116**(4):217-248.

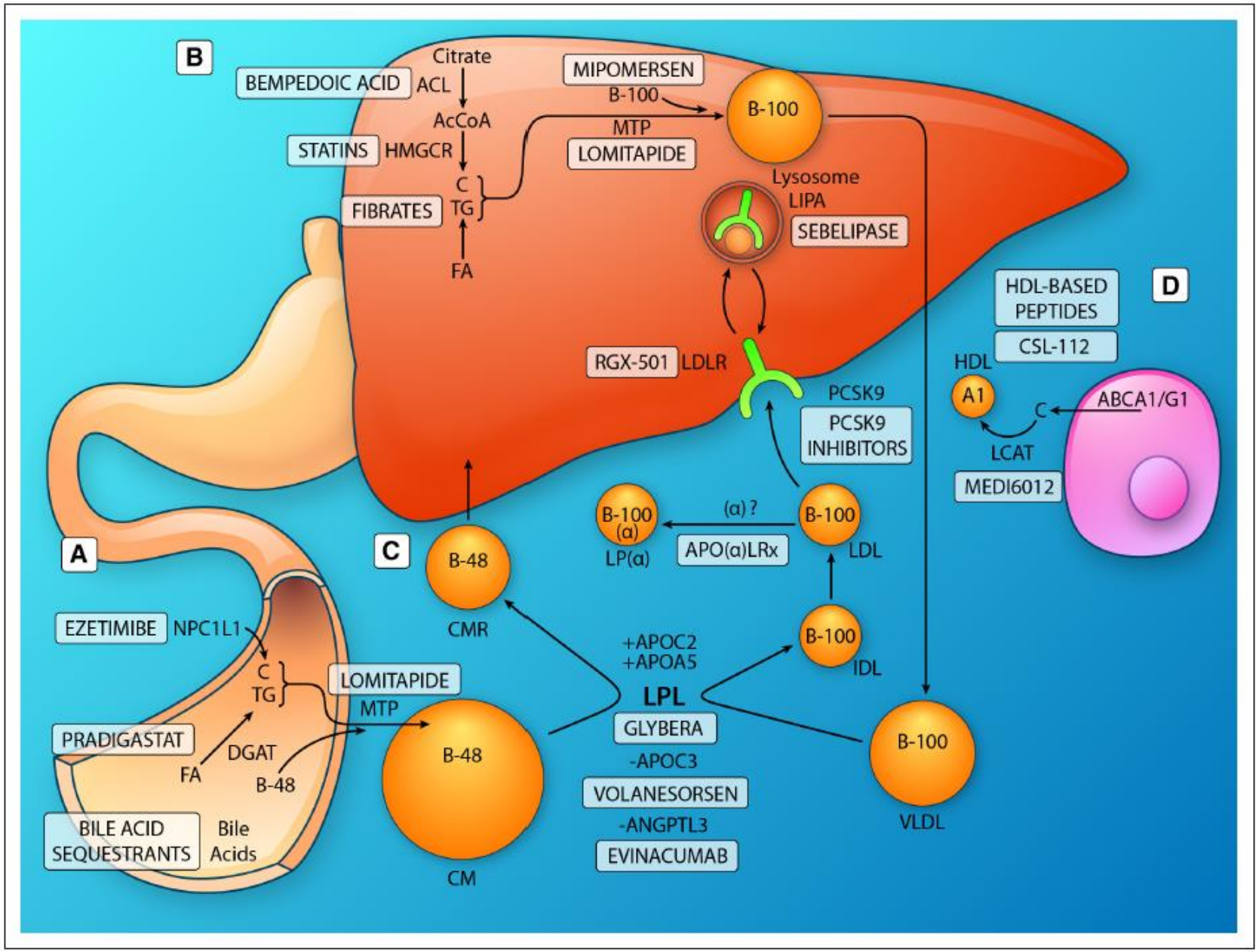


Prevalence of hyperlipidemia in adult DM ≈ 14.4%

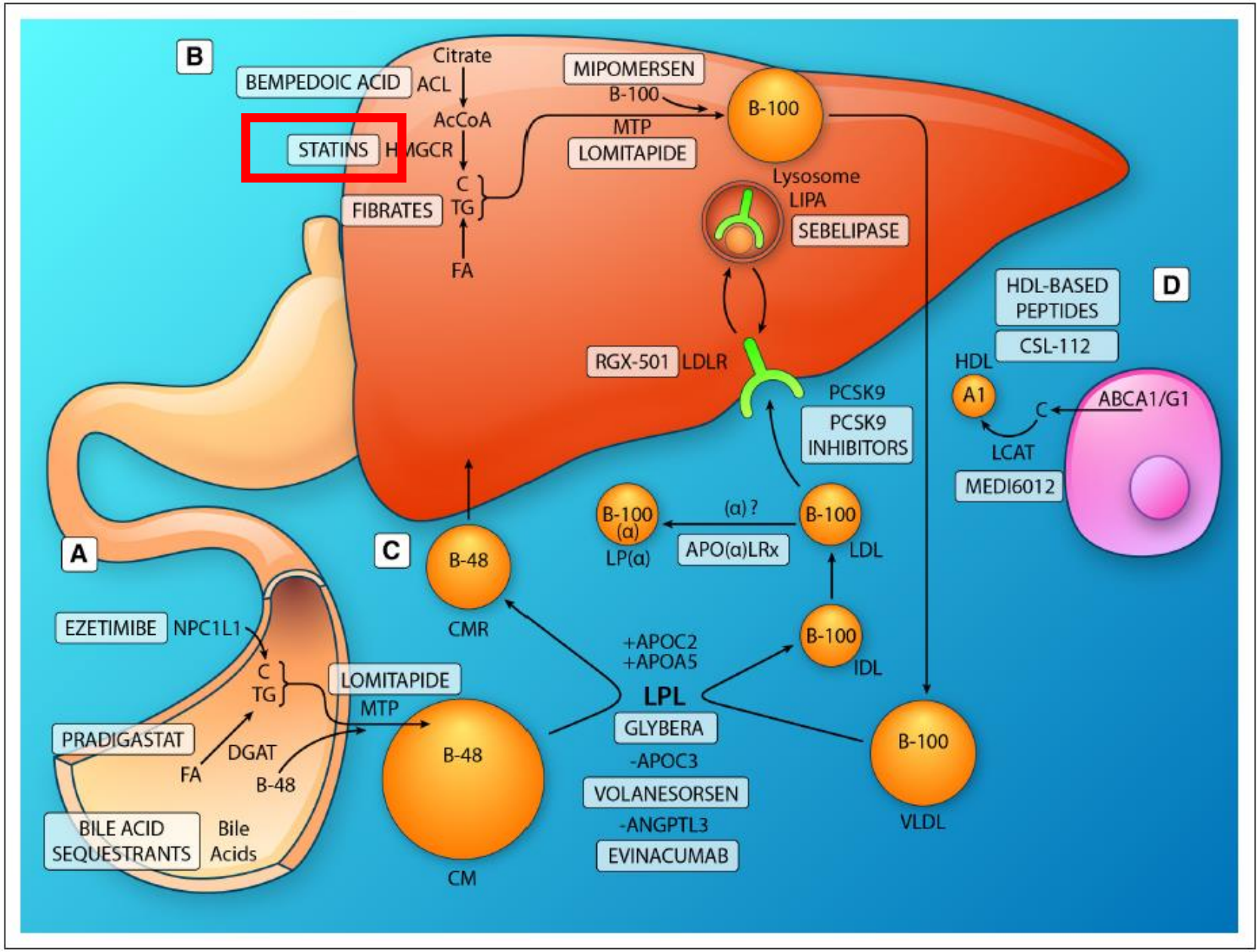
Lin, et al. *Journal of the Chinese Medical Association.* 2012; **116**(4):567-572.



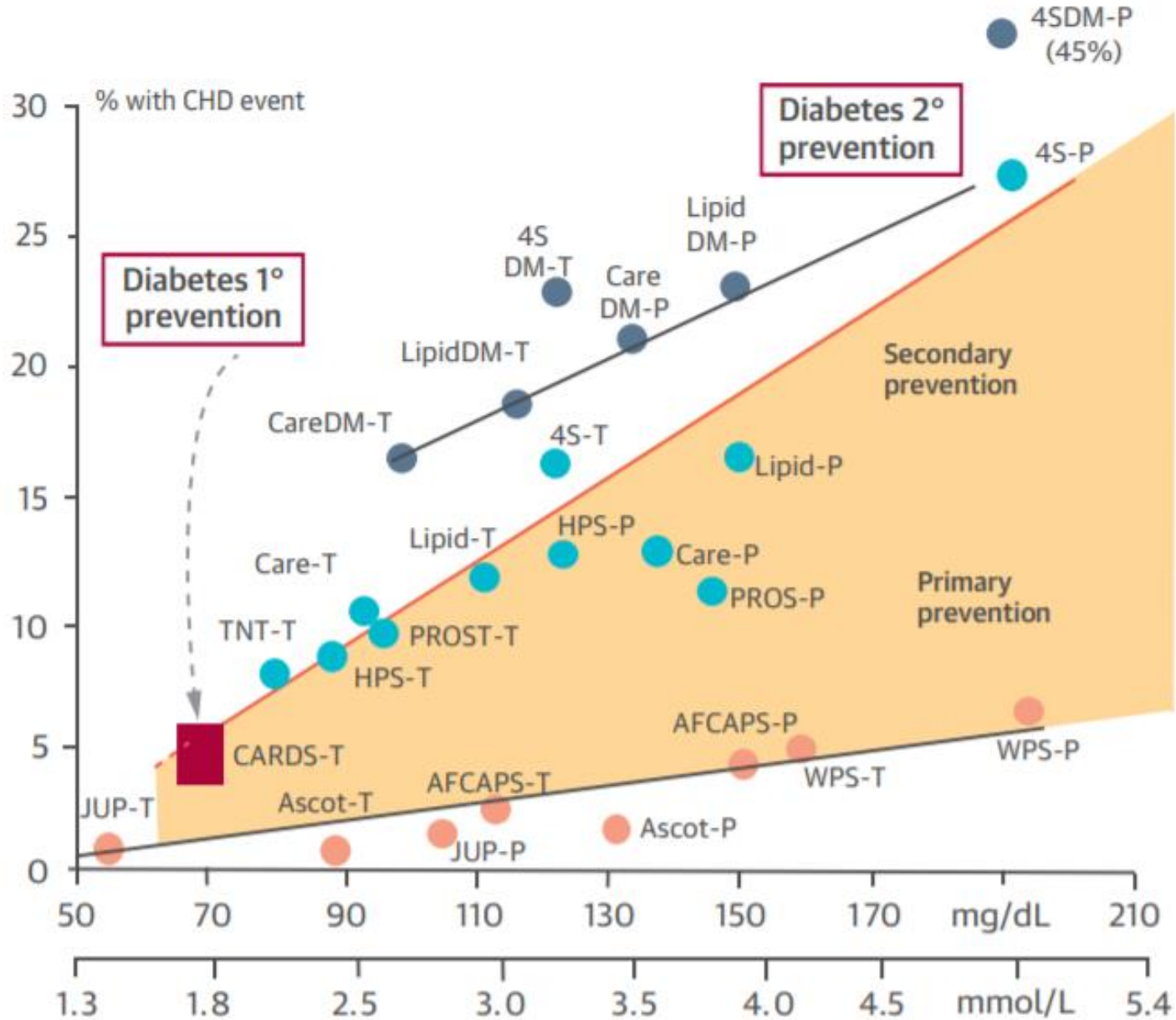
Mooradian. *Nat Clin Pract Endocrinol Metab.* 2009; **5**(3):150-9.



Hegele, et al. *Circ Res.* 2019; **124**:386-404.



Hegele, et al. *Circ Res.* 2019; **124**:386-404.



Opie. *J Am Coll Cardiol.* 2015; **66**(12):1412-3.

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

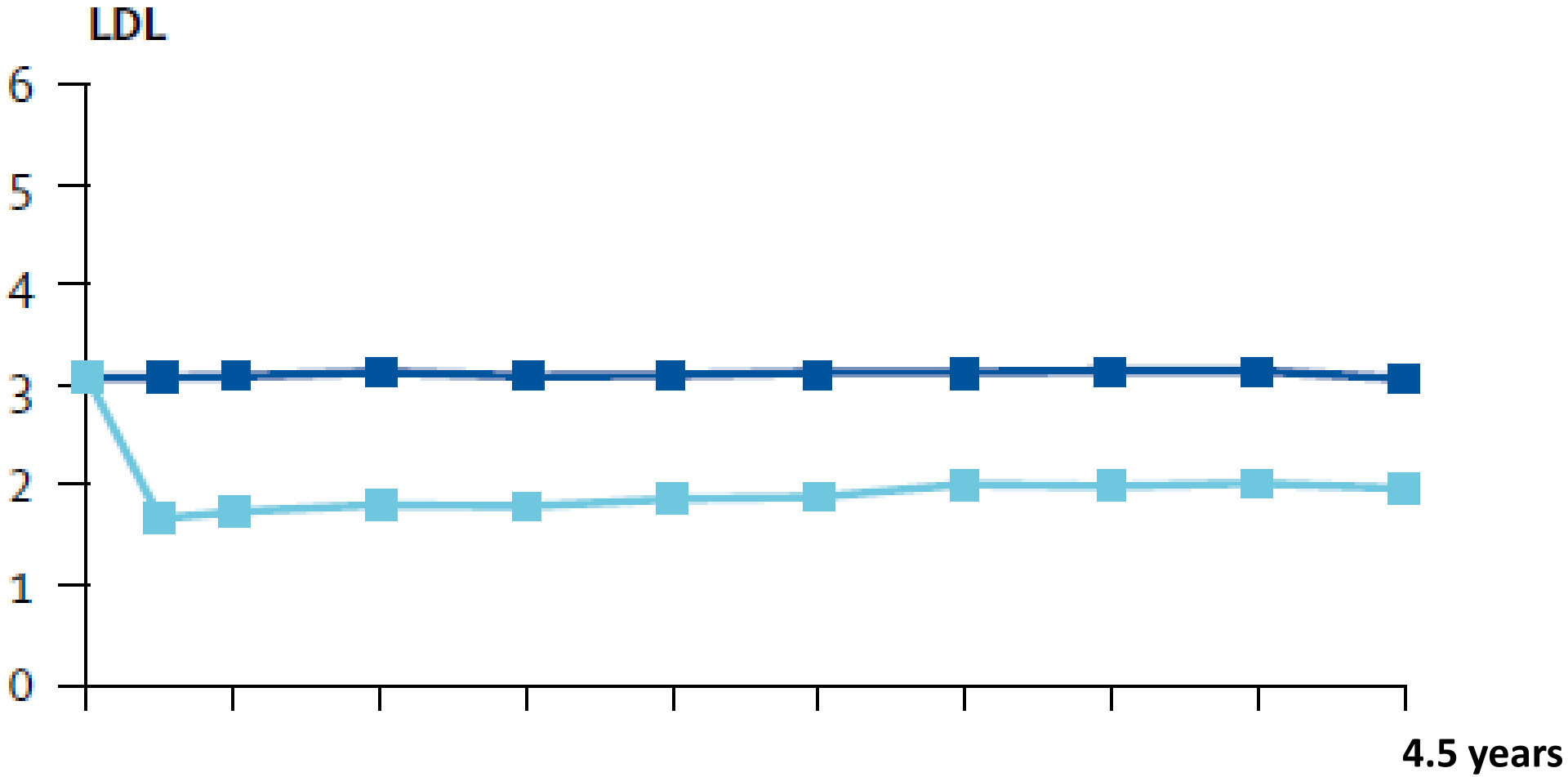
*Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingstone, Margaret J Thomason, Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators**

Lancet 2004; 364: 685–96

See Comment page 641

	Placebo (n=1410)	Atorvastatin (n=1428)
Demographics		
Age (years)	61·8 (8·0)	61·5 (8·3)
Age <60 years	529 (38%)	558 (39%)
Age 60–70 years	708 (50%)	703 (49%)
Age >70 years	173 (12%)	167 (12%)
Women	453 (32%)	456 (32%)
White ethnic origin	1326 (94%)	1350 (95%)
Diabetes duration (years)	7·8 (6·33)	7·9 (6·36)
Lipids		
Total cholesterol (mmol/L)	5·35 (0·82)	5·36 (0·83)
LDL-cholesterol (mmol/L)	3·02 (0·70)	3·04 (0·72)
HDL-cholesterol (mmol/L)	1·42 (0·34)	1·39 (0·32)
Median (IQR) triglyceride (mmol/L)	1·67 (1·17–2·40)	1·70 (1·20–2·40)
Non-HDL cholesterol	3·93 (0·82)	3·96 (0·82)
Apolipoprotein A1 (mg/L)	1530 (294)	1530 (271)
Apolipoprotein B (mg/L)	1150 (241)	1170 (243)

Baseline LDL ≈ 116 mg/dl



Treatment LDL ≈ 68-82 mg/dl

Placebo LDL ≈ 116 mg/dl

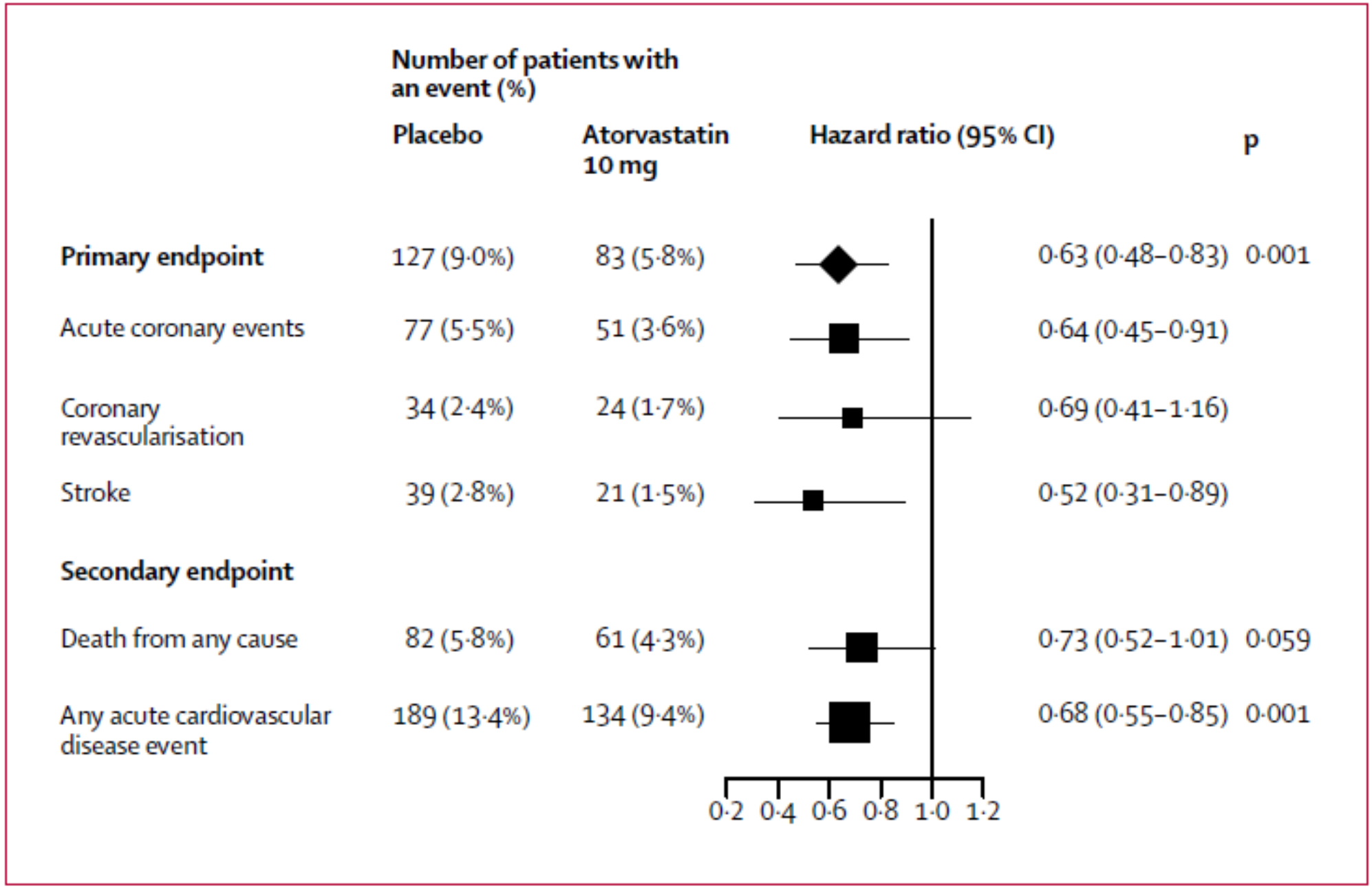

Number of patients with an event (%)
Placebo
Atorvastatin 10 mg
Hazard ratio (95% CI)
p
Primary endpoint
127 (9·0%)
83 (5·8%)
0·63 (0·48–0·83)
0·001
Acute coronary events
77 (5·5%)
51 (3·6%)
0·64 (0·45–0·91)
Coronary revascularisation
34 (2·4%)
24 (1·7%)
0·69 (0·41–1·16)
Stroke
39 (2·8%)
21 (1·5%)
0·52 (0·31–0·89)
Secondary endpoint
Death from any cause
82 (5·8%)
61 (4·3%)
0·73 (0·52–1·01)
0·059
Any acute cardiovascular disease event
189 (13·4%)
134 (9·4%)
0·68 (0·55–0·85)
0·001
0·2
0·4
0·6
0·8
1·0
1·2

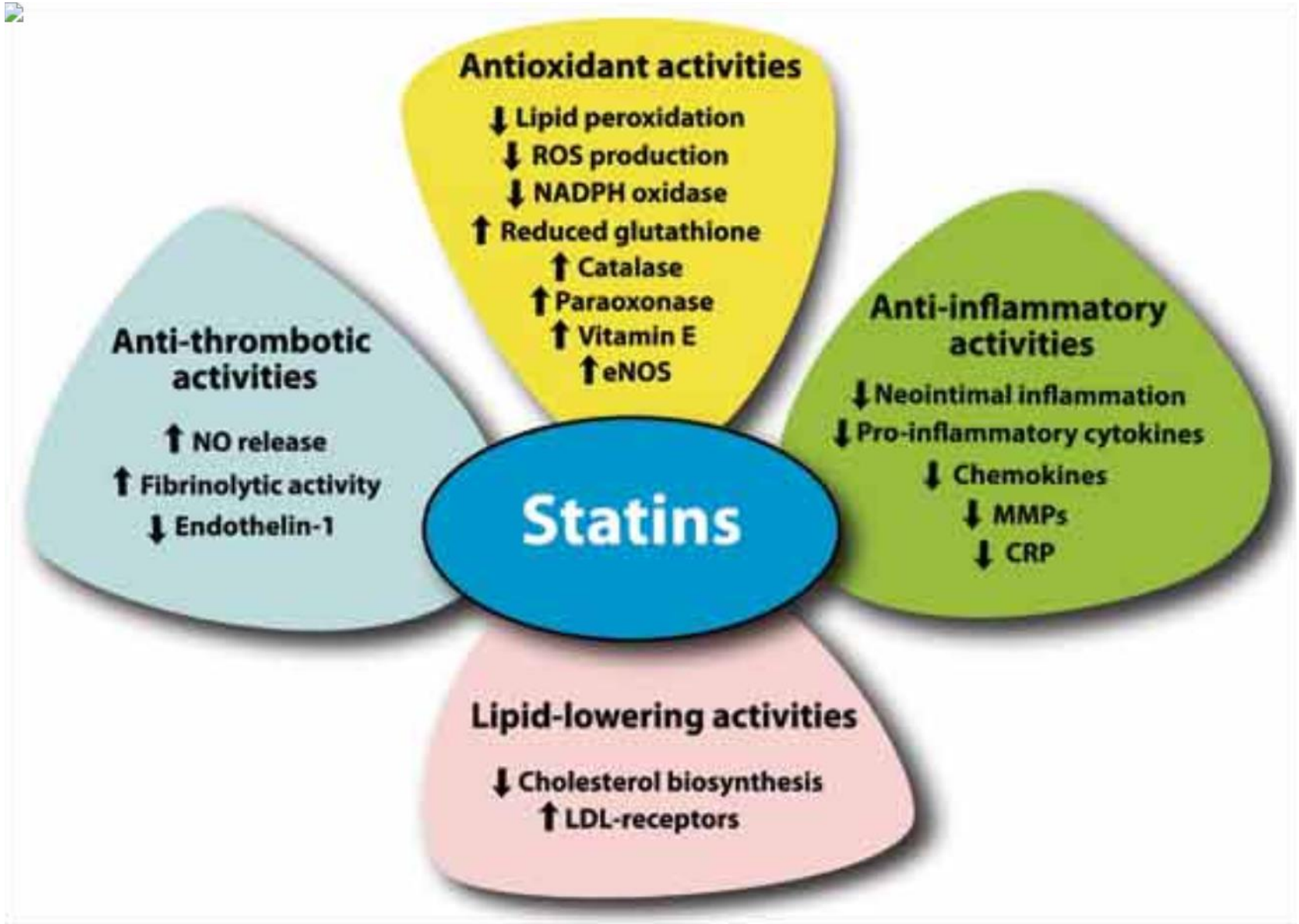
Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

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)

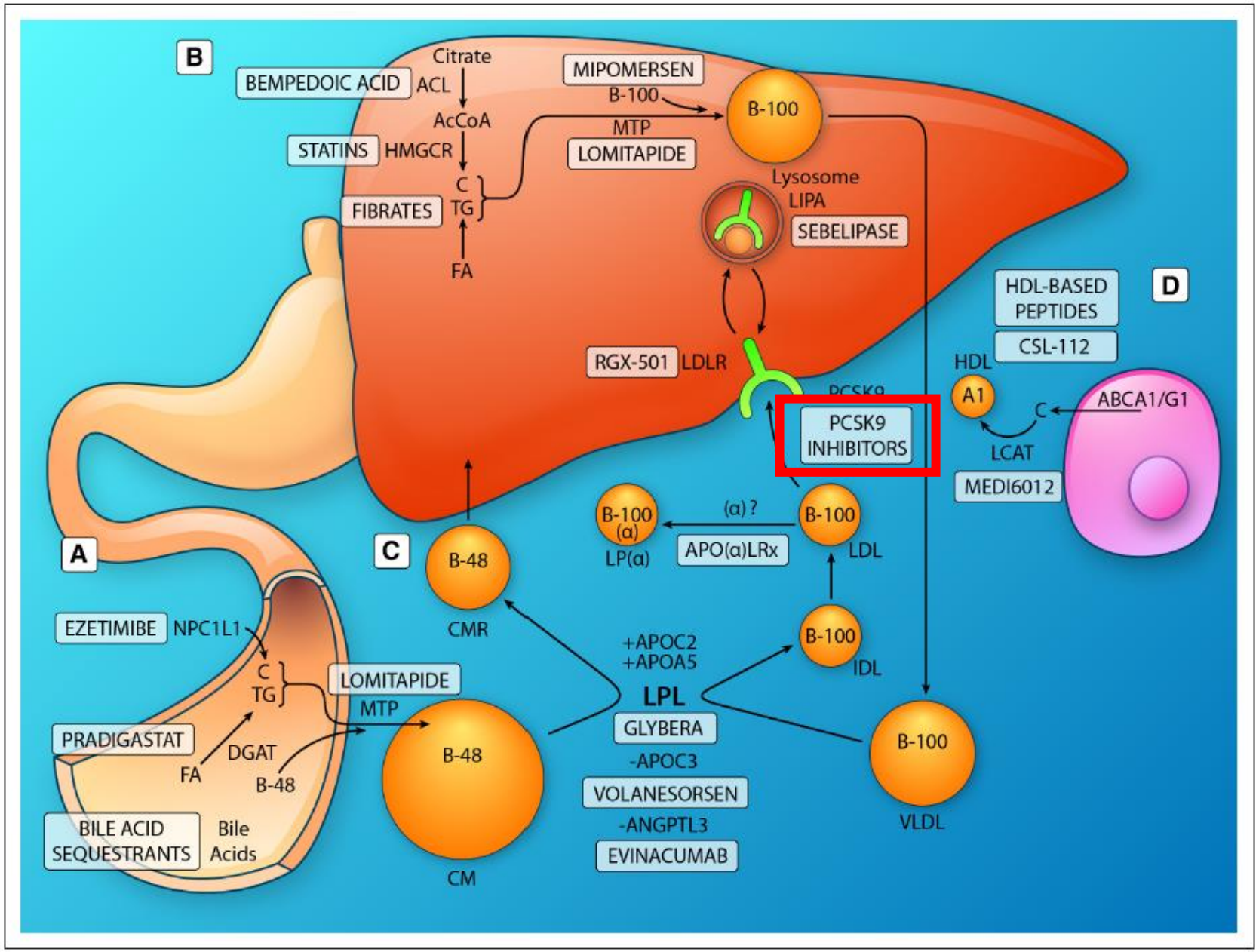
Table 10.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.



Profumo et al. *Curr Top Med Chem. 2014;**14**(22):2542-51.*



Hegele, et al. *Circ Res.* 2019; **124**:386-404.

Table 1 | **Percentage reduction in plasma LDL-C level with PCSK9-inhibitor therapy**

PCSK9 inhibitor	Dosing	Reduction in plasma LDL-C level with PCSK9 inhibition				
		As monotherapy	Added to statin therapy	In patients with statin intolerance	In patients with heterozygous FH	In patients with homozygous FH
Evolocumab	140 mg every 2 weeks or 420 mg monthly	55–57%[11]	63–75%[12]	55–56%[13,14]	60–66%[15]	31%[18]
Alirocumab	75 mg every 2 weeks, increased to150 mg if LDL-C level ≥70 mg/dl	47%[20]	46–51%[21,22]	45%[23]	58%[26,27]	ND
	300 mg every 4 weeks	59%[25]	56%[25]	ND	ND	ND
	150 mg every 2 weeks	ND	62%[24]	ND	39%[26,27]	ND

FH, familial hypercholesterolaemia; LDL-C, LDL cholesterol; ND, no data.

Sabatine. *Nat Rev Cardiol.* 2019; **16**(3):155-165.

Table 2 | **Effect of high-intensity statin therapy and PCSK9-inhibitor therapy on levels of clinical plasma parameters**

Therapy	LDL-C level	HDL-C level	Triglyceride level	Apolipoprotein B level	Lipoprotein (a) level	High-sensitivity CRP level
High-intensity statin	↓ 50–60%	↑ 5–10%	↓ 25–35%	↓ 40–50%	↔ / ↑	↓ ~35%
Ezetimibe	↓ 20–25%	↔	↓ 5–10%	↓ 15–20%	↓ ~10%	↓ 15–20%
PCSK9 inhibitor	↓ ~60%	↑ 5–10%	↓ ~15%	↓ ~50%	↓ ~25%	↔

CRP, C-reactive protein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

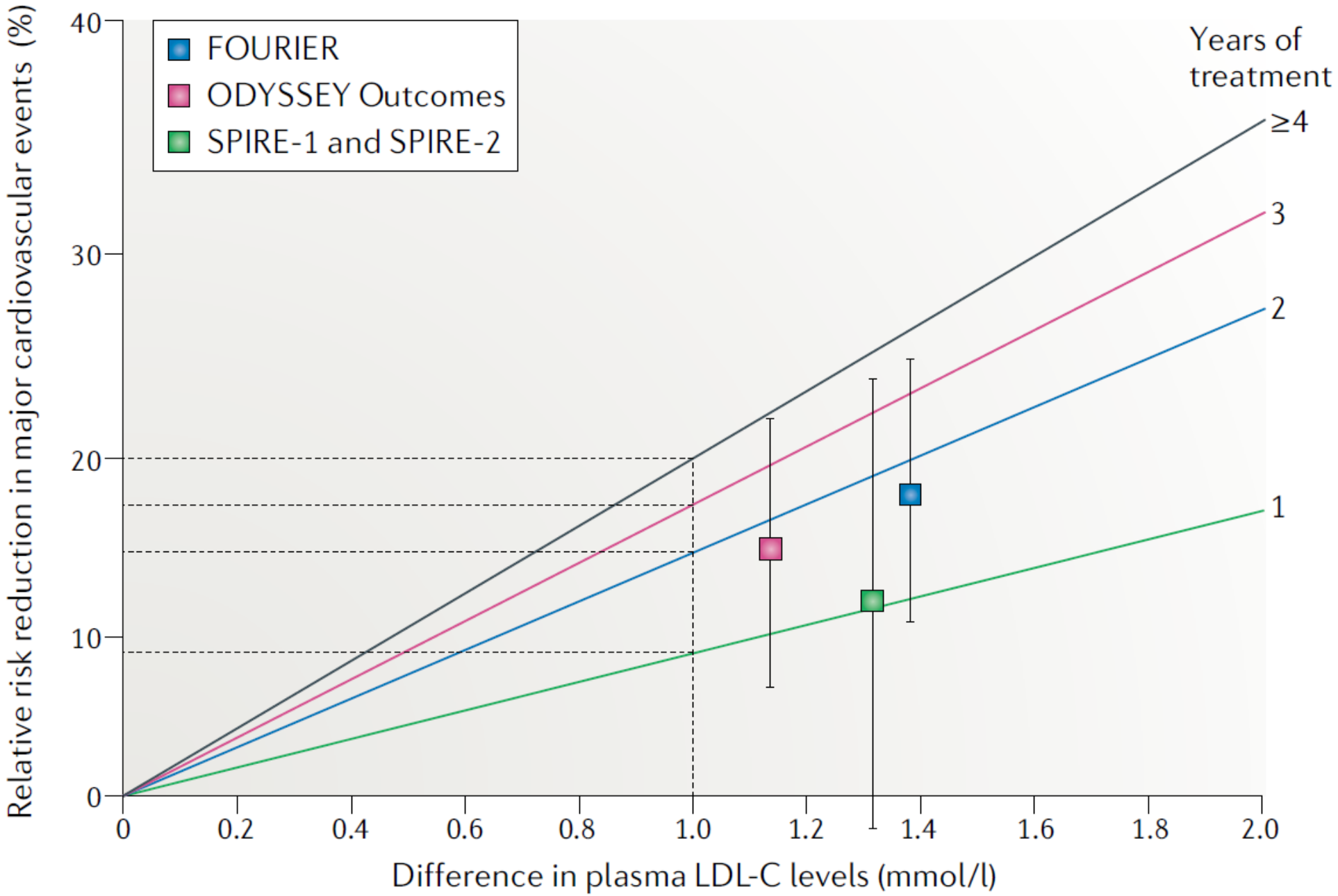
Sabatine. *Nat Rev Cardiol.* 2019; **16**(3):155-165.

Table 3 | **Summary of the placebo-controlled cardiovascular outcome trials on PCSK9 inhibitors**

PCSK9 inhibitor	Trial name	Number of patients	Type of patients	Time from MI or stroke	Patients receiving high-intensity statin therapy (%)	Baseline LDL-C level (mg/dl)	Dosing of PCSK9 inhibitor	Mean absolute reduction in plasma LDL-C level (mg/dl)	Median follow-up	Outcomes (primary end point and main secondary end point)	Refs
Evolocumab	FOURIER	27,564	Patients with MI, stroke or PAD	~3 years	69	92	140 mg every 2 weeks or 420 mg every 4 weeks	56	2.2 years	CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization: HR 0.85 (95% CI 0.79–0.92); CV death, MI or stroke: HR 0.80 (95% CI 0.73–0.88)	30,34
Alirocumab	ODYSSEY Outcomes	18,924	Patients with history of ACS	4–52 weeks (median 2.6 months)	89	87	75 mg or 150 mg every 2 weeks (titrated to achieve LDL-C 25–50 mg/dl)	37–48[a]	2.8 years	CHD death, MI, ischaemic stroke or hospitalization for unstable angina: HR 0.85 (95% CI 0.78-0.93)	45,46
Bococizumab	SPIRE-1	16,817	Patients in secondary prevention of CVD (84%) or high-risk patients in primary prevention of CVD (16%)	NA	92	94	150 mg every 2 weeks (titrated down if plasma LDL-C level <10 mg/dl)	54	7 months	CV death, MI, stroke or urgent revascularization: HR 0.99 (95% CI 0.80–1.22)	43,44
Bococizumab	SPIRE-2	10,621	Patients in secondary prevention of CVD (84%) or high-risk patients in primary prevention of CVD (16%)	NA	73	134	150 mg every 2 weeks (titrated down if plasma LDL-C level <10 mg/dl)	67	12 months	CV death, MI, stroke or urgent revascularization: HR 0.79 (95% CI 0.65–0.97)	43,44

ACS, acute coronary syndrome; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; NA, not available; PAD, peripheral artery disease. [a]From 12 to 48 months.

Sabatine. *Nat Rev Cardiol.* 2019; **16**(3):155-165.



Sabatine. *Nat Rev Cardiol.* 2019; **16**(3):155-165.

Drug	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Metformin	↓ ↔	↓	↔ ↑	↓ ↔
Gliclazide	↓	↔	↔	↓
Glimepiride	↔	↔	↔ ↑	↔
Pioglitazone	↑	↔	↑	↓
Sitagliptin	↔	↔	↔ ↑	↔
Saxagliptin	↔	↔	↔	↔
Vildagliptin	↔	↔	↔ ↑	↔
Linagliptin	↔	↔	↔	↔
Dapagliflozin	↔ ↑	↔ ↑	↔ ↑	↓ ↔
Canagliflozin	↑	↑	↑	↑
Empagliflozin	↔ ↑	↔ ↑	↔ ↑	↔
Exenatide	↓ ↔	↔ ↑	↔ ↑	↓
Liraglutide	↔	↔ ↓ (small, dense LDL)	↔	↓

↓ Decrease ↓ ↔ Slight decrease ↔ No change ↔ ↑ Slight increase ↑ Increase

Martín-Timón, et al. *EMJ Diabet.* 2018; **6**(1):53-61.

Journal of the Formosan Medical Association (2017) 116, 217–248

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journal homepage: www.jfma-online.com

REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

Yi-Heng Li [a], Kwo-Chang Ueng [b,c], Jiann-Shing Jeng [d], Min-Ji Charng [e,f], Tsung-Hsien Lin [g,h], Kuo-Liong Chien [i,j], Chih-Yuan Wang [j], Ting-Hsing Chao [a], Ping-Yen Liu [a], Cheng-Huang Su [k,l], Shih-Chieh Chien [k], Chia-Wei Liou [m], Sung-Chun Tang [d], Chun-Chuan Lee [k], Tse-Ya Yu [n], Jaw-Wen Chen [e,f,o], Chau-Chung Wu [j], Hung-I Yeh [k,l,*], for The Writing Group of 2017 Taiwan Lipid Guidelines for High Risk Patients

Table 9 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 y 2. Diabetic patients aged <40 y who have overt ASCVD or ASCVD risk factors	ASCVD risk factors include: - High blood pressure - Smoking - Overweight and obesity - Family history of premature ASCVD

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

表一、糖尿病人血脂目標

主要目標		說明
低密度脂蛋白膽固醇	所有病人 <100 mg/dl 已有心血管疾病 <70 mg/dl	建議使用中 / 強效果的 statins 為第一線藥物治療
高密度脂蛋白膽固醇	男 >40 mg/dl 女 >50 mg/dl	生活型態介入治療及血糖控制為優先
三酸甘油酯	<150 mg/dl	血糖控制及生活型態介入治療為優先。但三酸甘油酯 ≥500 mg/dl，需給 fibrates
次要目標		
非高密度脂蛋白膽固醇	所有病人 <130 mg/dl 已有心血管疾病 <100 mg/dl	當主要目標達成時，再評估次要目標

2018 糖尿病臨床照護指引

健保降血脂藥物給付規定

108年2月1日起

	藥物治療	起始藥物血脂值 (控制目標為小於起始值)
• 有急性冠狀動脈症候群病史 • 曾接受心導管介入或CABG之冠狀動脈粥狀硬化患者	與藥物治療可並行	LDL-C ≧ 70mg/dL
心血管疾病或糖尿病患者		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
1 個危險因子		TC ≧ 240mg/dL 或 LDL-C ≧ 160mg/dL
0 個危險因子		LDL-C ≧ 190mg/dL

風險因子定義

- 高血壓
- 男性 ≧ 45 歲，女性 ≧ 55 歲或停經者
- 有早發性冠心病家族史（男性 ≦ 55 歲，女性 ≦ 65 歲）
- HDL-C < 40 mg/dL
- 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）。

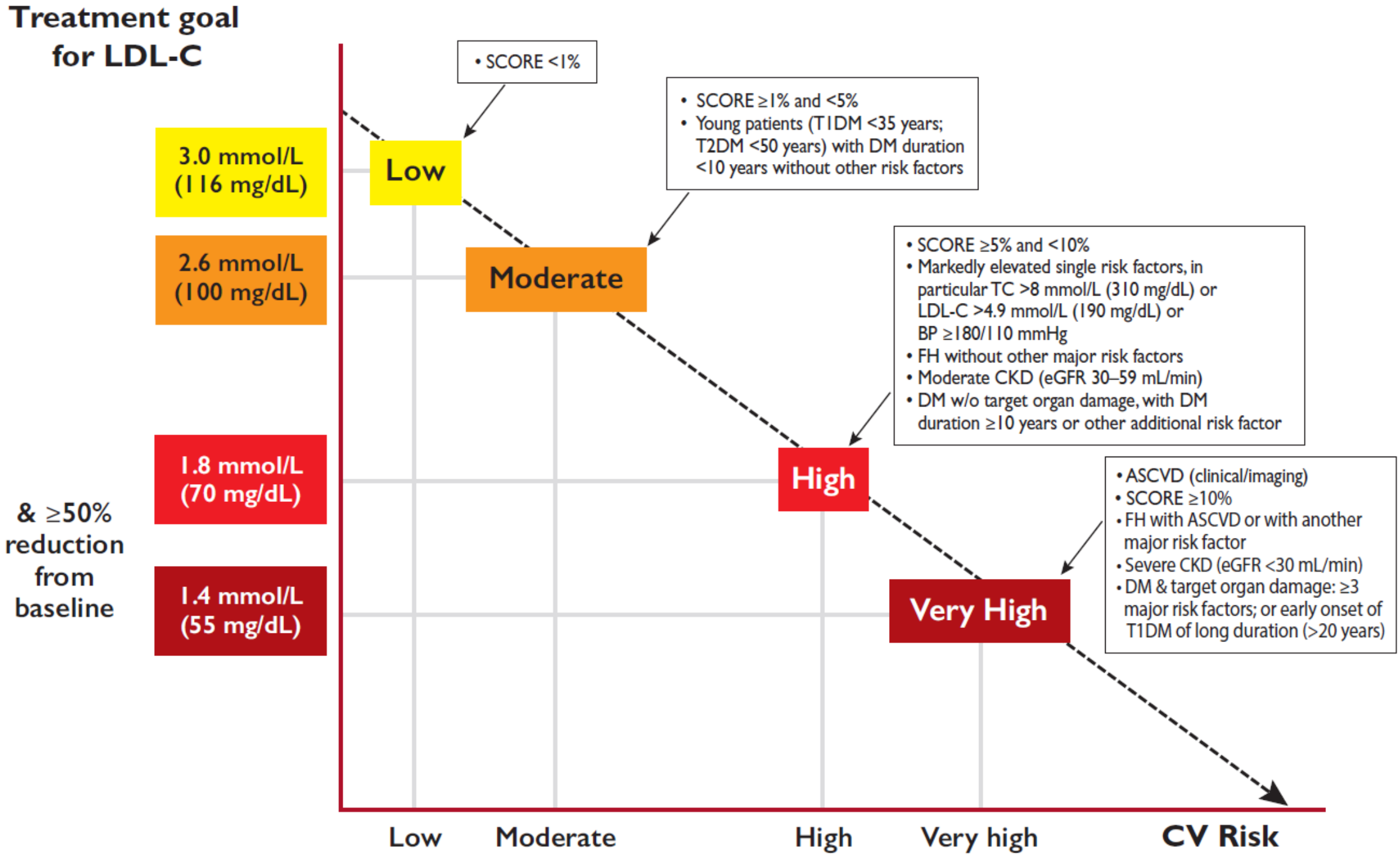
ESC European Society of Cardiology

European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)


Treatment goal for LDL-C
3.0 mmol/L (116 mg/dL)
2.6 mmol/L (100 mg/dL)
1.8 mmol/L (70 mg/dL)
1.4 mmol/L (55 mg/dL)
& ≥50% reduction from baseline
• SCORE <1%
Low
• SCORE ≥1% and <5%
• Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
Moderate
• SCORE ≥5% and <10%
• Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
• FH without other major risk factors
• Moderate CKD (eGFR 30–59 mL/min)
• DM w/o target organ damage, with DM duration ≥10 years or other additional risk factor
High
• ASCVD (clinical/imaging)
• SCORE ≥10%
• FH with ASCVD or with another major risk factor
• Severe CKD (eGFR <30 mL/min)
• DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)
Very High
Low
Moderate
High
Very high
CV Risk

“The lower LDL, the better.”

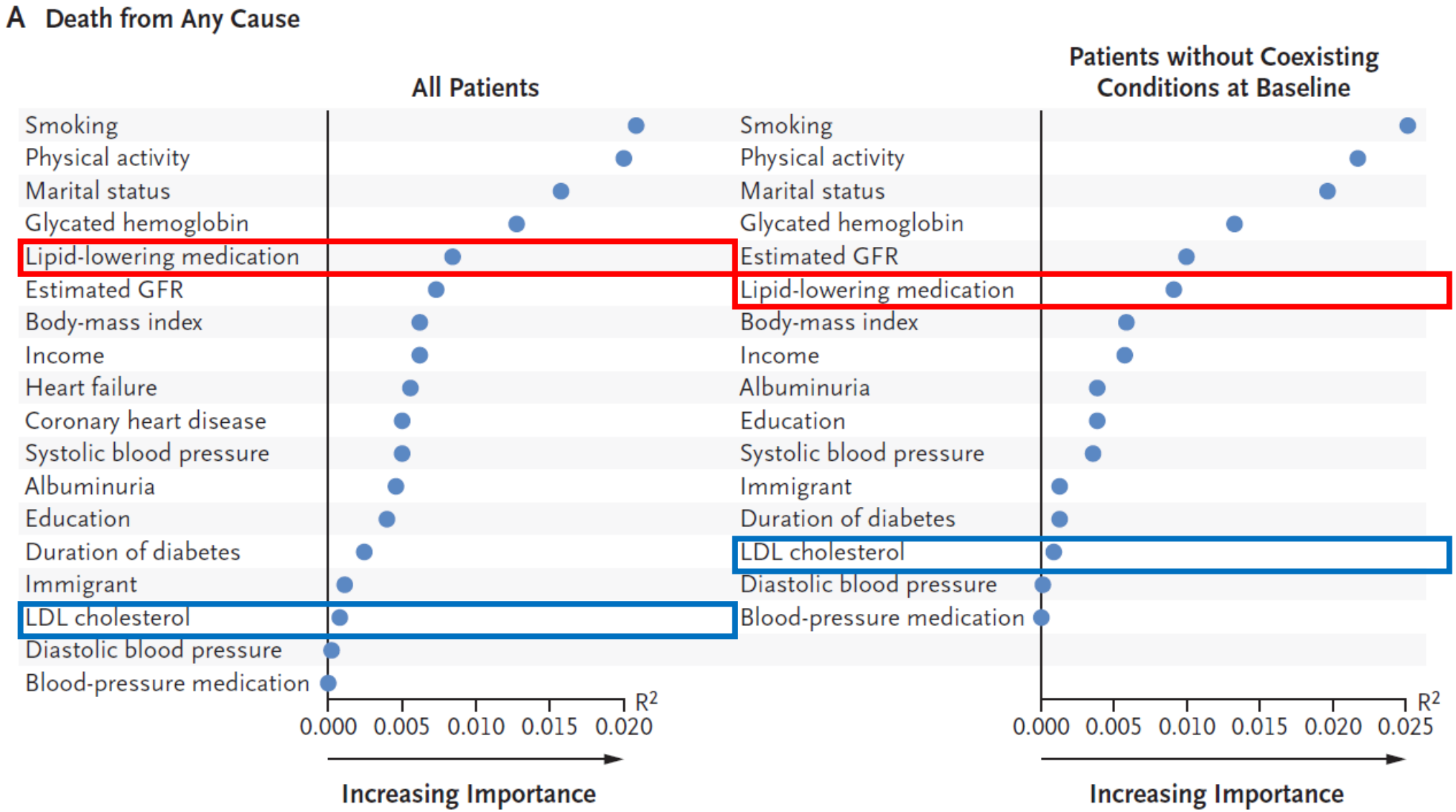
…… for *ALL?*

The NEW ENGLAND JOURNAL of MEDICINE

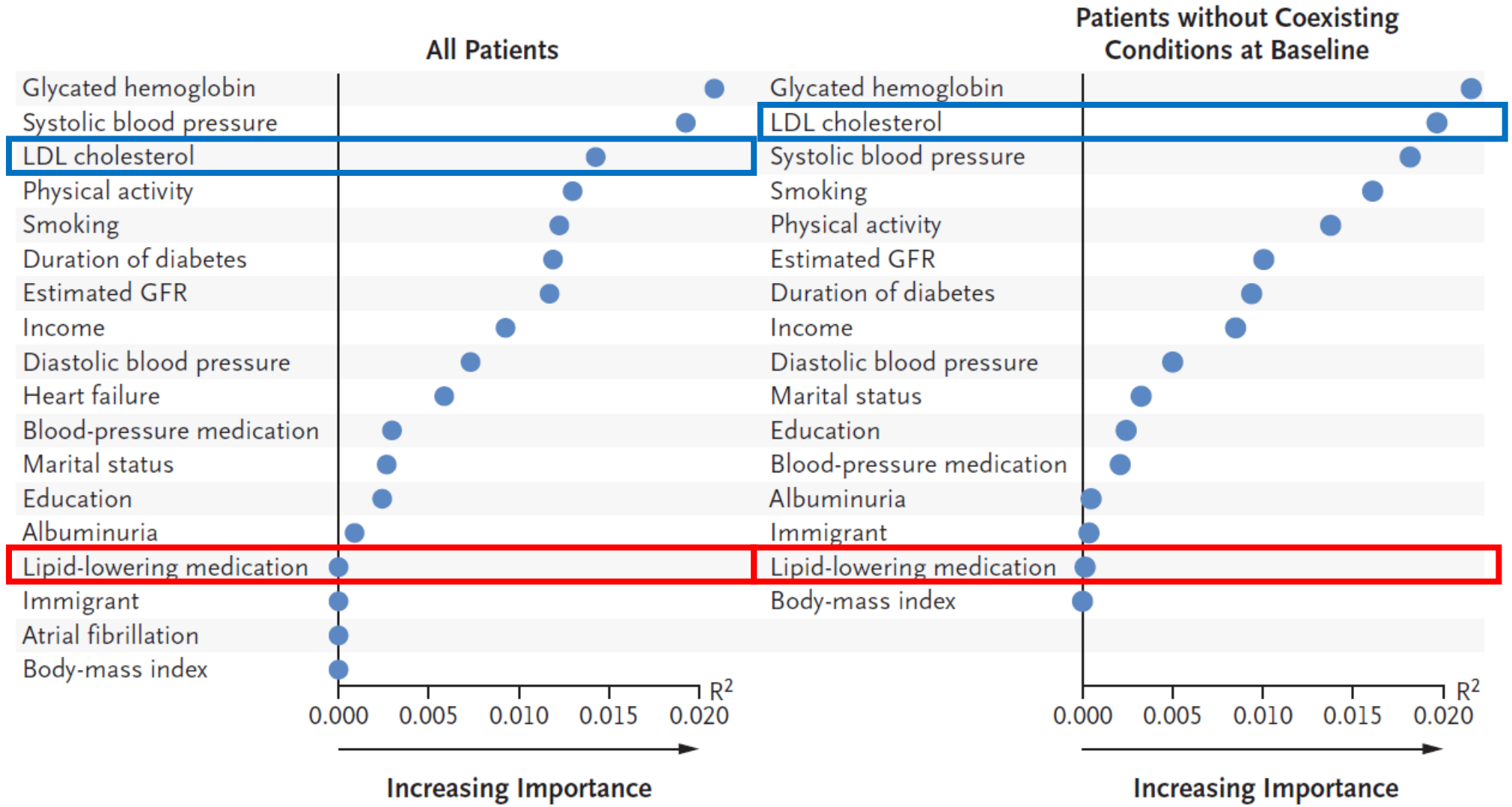
ORIGINAL ARTICLE

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

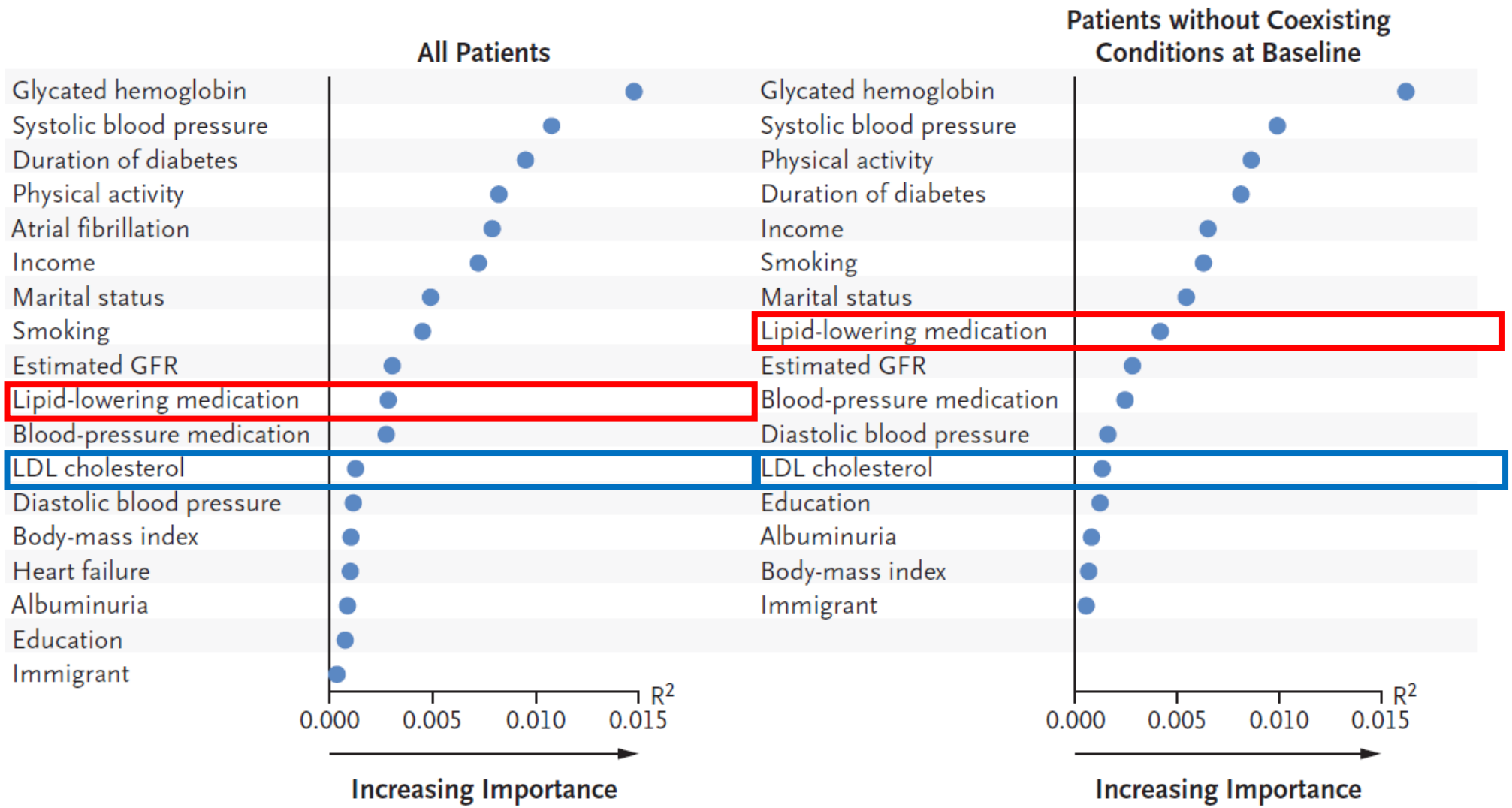
Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Naveed Sattar, M.D., Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Björn Zethelius, M.D., Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.


A Death from Any Cause
All Patients
Smoking
Physical activity
Marital status
Glycated hemoglobin
Lipid-lowering medication
Estimated GFR
Body-mass index
Income
Heart failure
Coronary heart disease
Systolic blood pressure
Albuminuria
Education
Duration of diabetes
Immigrant
LDL cholesterol
Diastolic blood pressure
Blood-pressure medication
R2
0.000 0.005 0.010 0.015 0.020
Increasing Importance
Patients without Coexisting Conditions at Baseline
Smoking
Physical activity
Marital status
Glycated hemoglobin
Estimated GFR
Lipid-lowering medication
Body-mass index
Income
Albuminuria
Education
Systolic blood pressure
Immigrant
Duration of diabetes
LDL cholesterol
Diastolic blood pressure
Blood-pressure medication
R2
0.000 0.005 0.010 0.015 0.020 0.025
Increasing Importance

B Acute Myocardial Infarction



C Stroke


All Patients
Glycated hemoglobin
Systolic blood pressure
Duration of diabetes
Physical activity
Atrial fibrillation
Income
Marital status
Smoking
Estimated GFR
Lipid-lowering medication
Blood-pressure medication
LDL cholesterol
Diastolic blood pressure
Body-mass index
Heart failure
Albuminuria
Education
Immigrant
0.000
0.005
0.010
0.015
R^2
Increasing Importance
Patients without Coexisting Conditions at Baseline
Glycated hemoglobin
Systolic blood pressure
Physical activity
Duration of diabetes
Income
Smoking
Marital status
Lipid-lowering medication
Estimated GFR
Blood-pressure medication
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LDL cholesterol
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Immigrant
0.000
0.005
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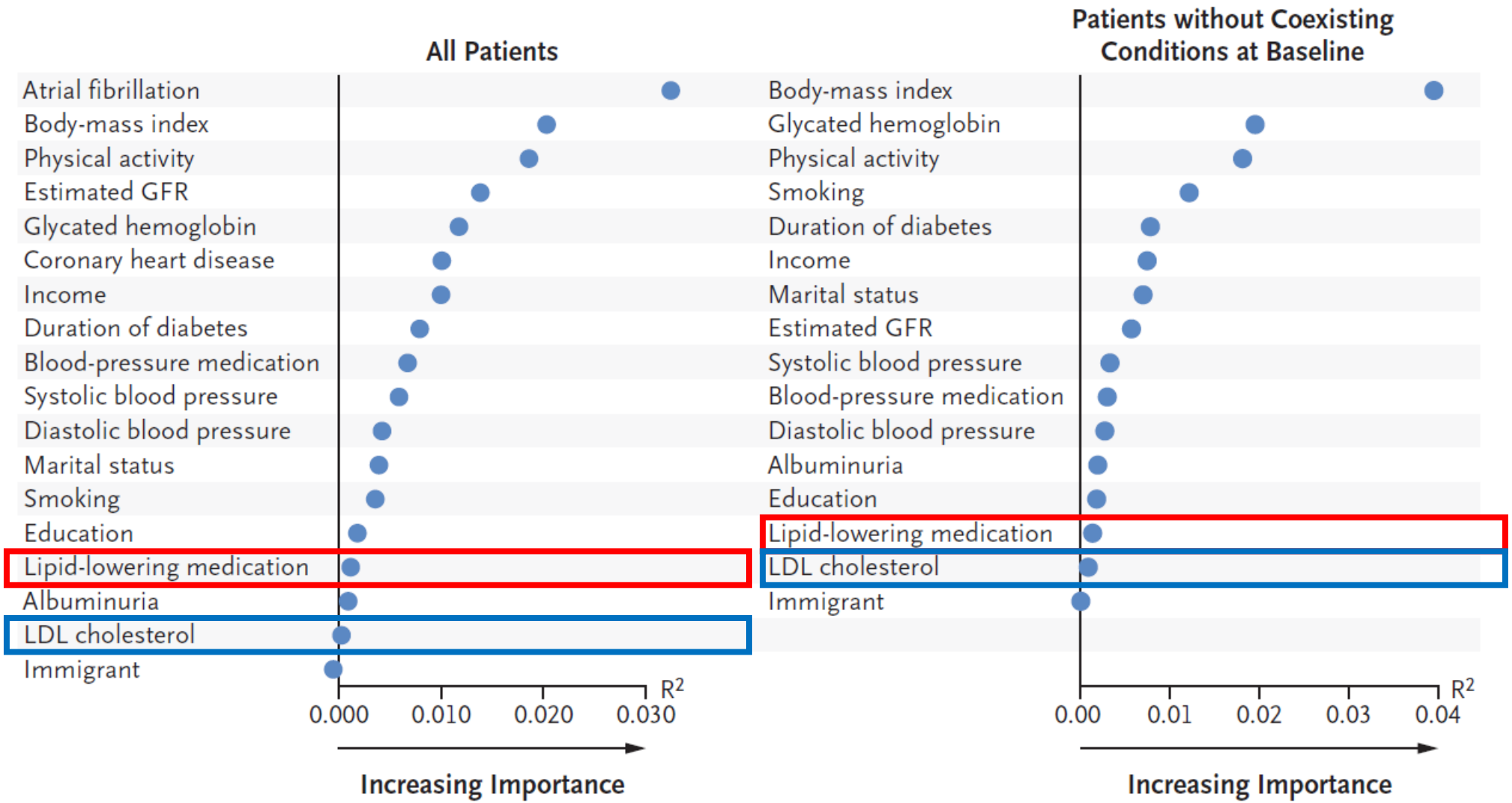
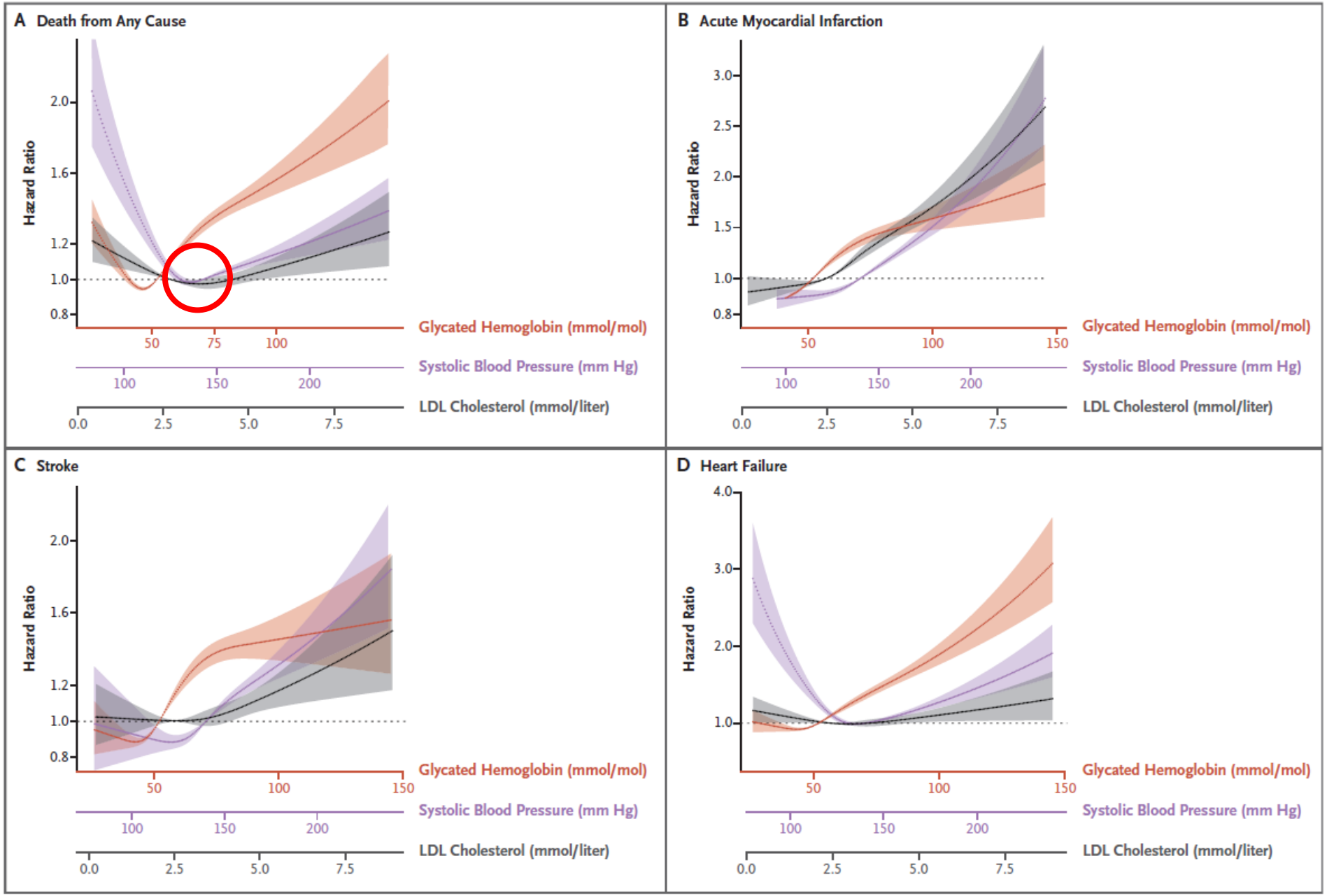
0.015
R^2
Increasing Importance

D Heart Failure




A Death from Any Cause
Hazard Ratio
2.0
1.6
1.2
1.0
0.8
Glycated Hemoglobin (mmol/mol)
50
75
100
Systolic Blood Pressure (mm Hg)
100
150
200
LDL Cholesterol (mmol/liter)
0.0
2.5
5.0
7.5
B Acute Myocardial Infarction
Hazard Ratio
3.0
2.5
2.0
1.5
1.0
0.8
Glycated Hemoglobin (mmol/mol)
50
100
150
Systolic Blood Pressure (mm Hg)
100
150
200
LDL Cholesterol (mmol/liter)
0.0
2.5
5.0
7.5
C Stroke
Hazard Ratio
2.0
1.6
1.2
1.0
0.8
Glycated Hemoglobin (mmol/mol)
50
100
150
Systolic Blood Pressure (mm Hg)
100
150
200
LDL Cholesterol (mmol/liter)
0.0
2.5
5.0
7.5
D Heart Failure
Hazard Ratio
4.0
3.0
2.0
1.0
Glycated Hemoglobin (mmol/mol)
50
100
150
Systolic Blood Pressure (mm Hg)
100
150
200
LDL Cholesterol (mmol/liter)
0.0
2.5
5.0
7.5

Conclusion

- Evidences support that active and sustained LDL-lowering management is beneficiary for patients with T2DM
- “The lower LDL, the better” theory might be outcome-specific.
- Further investigations are required to identify the eligible population for extreme-low LDL target.

Thanks for your attention!