Evidences of Statins on Cardiovascular and Renal Outcomes in Patients with Diabetes

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Outline

1

Diabetes

Introduction of diabetes and **diabetic dyslipidemia**.

2

Global

Global: Statin trials in diabetic patients.

3

Asia - Taiwan

Asia and Taiwan: Statin trials in diabetic patients.

4

Safety

Safety of statin in diabetic patients.

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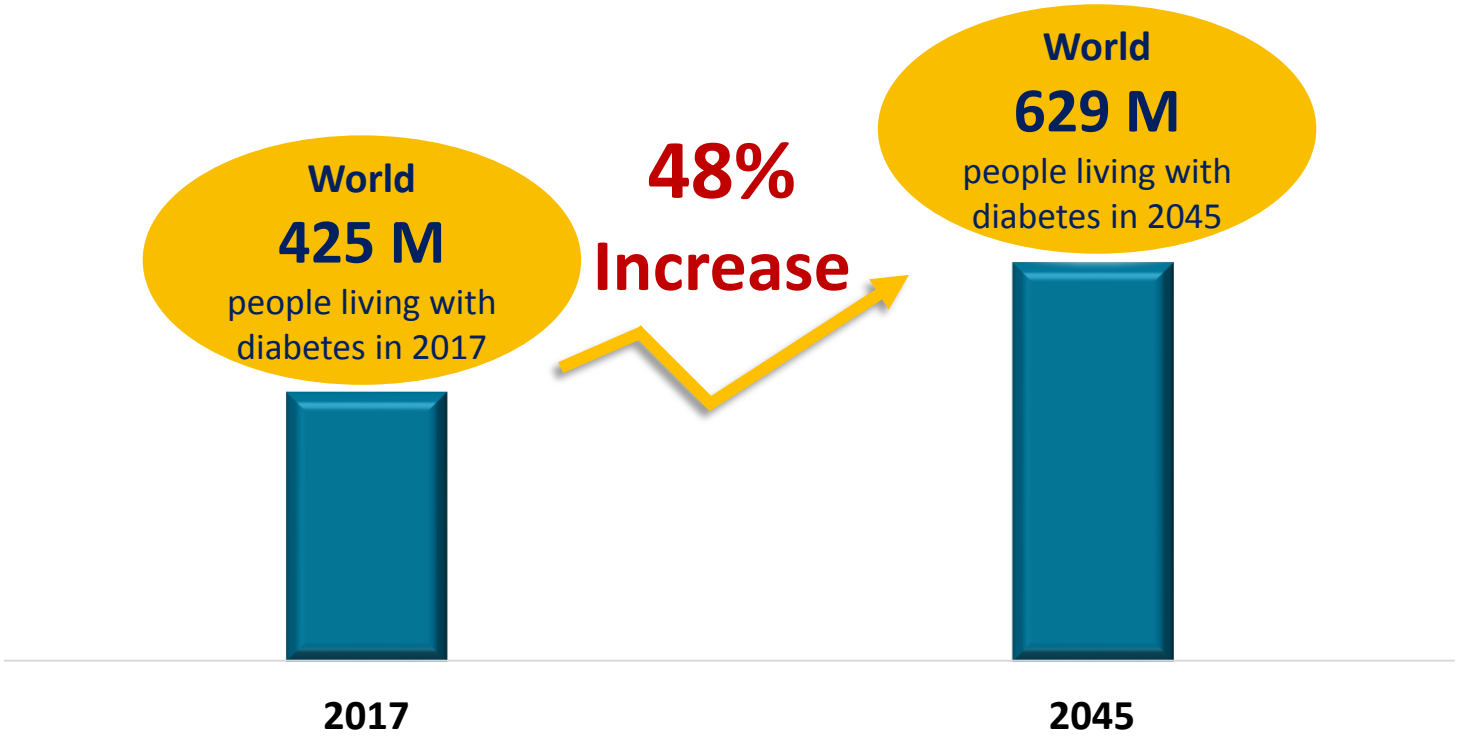
Diagnostic criteria for diabetes mellitus

Diagnosis/ measurement	WHO 2006[3]/2011[4]	ADA 2019[5]
DM		
	Can be used	**Recommended**
HbA1c	If measured, ≥6.5% (48 mmol/mol)	≥6.5% (48 mmol/mol)
	Recommended	
FPG	≥7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
	or	**or**
2hPG	≥11.1 mmol/L (≥200 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
RPG	Symptoms plus ≥11.1 mmol/L (≥200 mg/dL)	Symptoms plus ≥11.1 mmol/L (≥200 mg/dL)

Global epidemiology of diabetes

Growing population of diabetes has become a global burden. In 2017, diabetic population reached 425 million (M).



International Diabetes Federation. IDF diabetes atlas. 8th edition. 2017.

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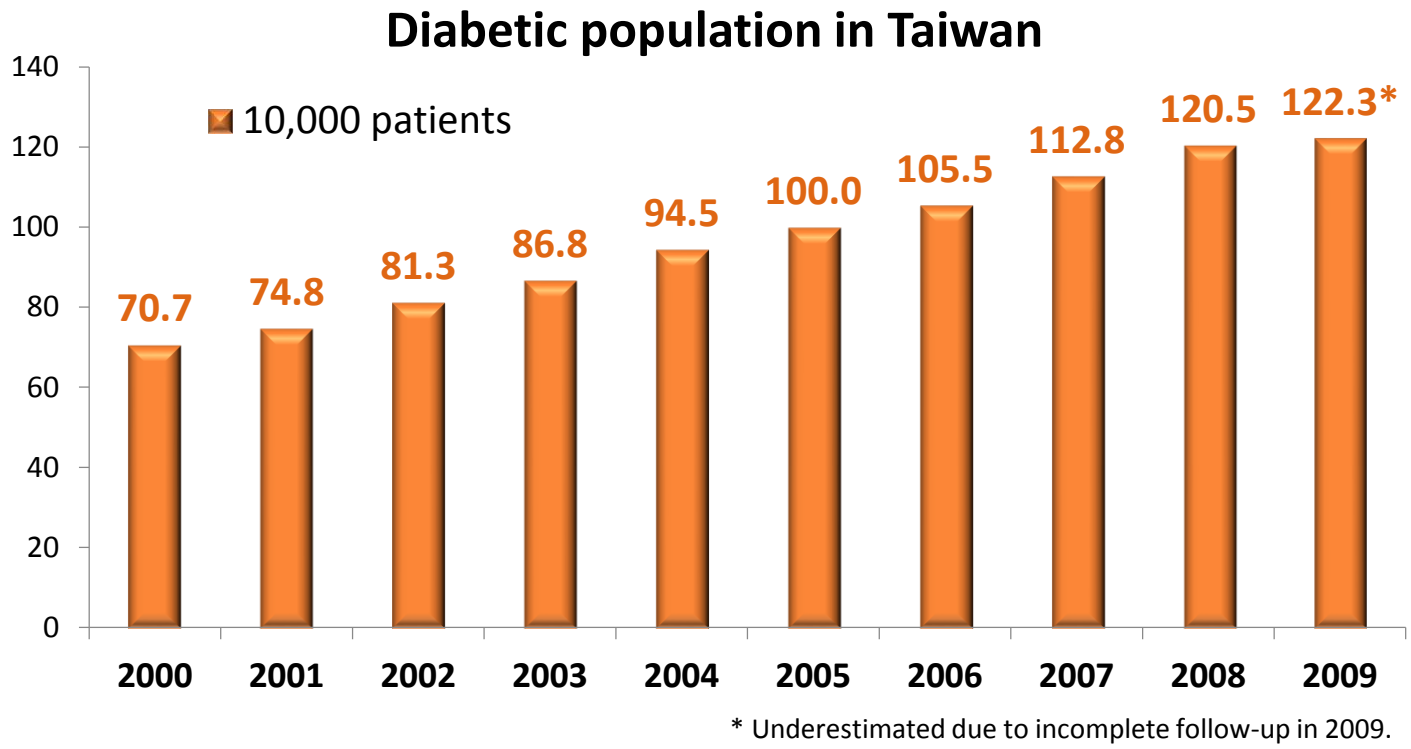
Epidemiology of diabetes in Taiwan

Diabetes

According to data from the National Health Insurance (NHI), diabetic population in Taiwan increased by more than 70% from 2000 to 2009.



* Underestimated due to incomplete follow-up in 2009.

J Formos Med Assoc. 2012;111(11):599-604.

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Microvascular & macrovascular complications

Diabetes

Microvascular

May be the most common microvascular complication;

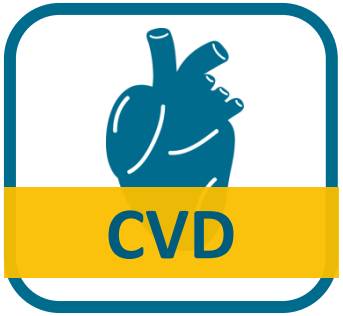
Caused ~10,000 **blindness** in US annually.

Defined by proteinuria > 500 mg in 24 hours;

Is the leading cause of **renal failure**.

The risk increases with the duration and magnitude of hyperglycemia.

Macrovascular



Framingham study demonstrated the association between diabetes and CVD.

Atherosclerosis and increased platelet adhesion and hypercoagulability contribute to the increased risk of CVD.

US: United States; CVD: cardiovascular disease.

Clinical Diabetes. 2008;26(2):77-82.

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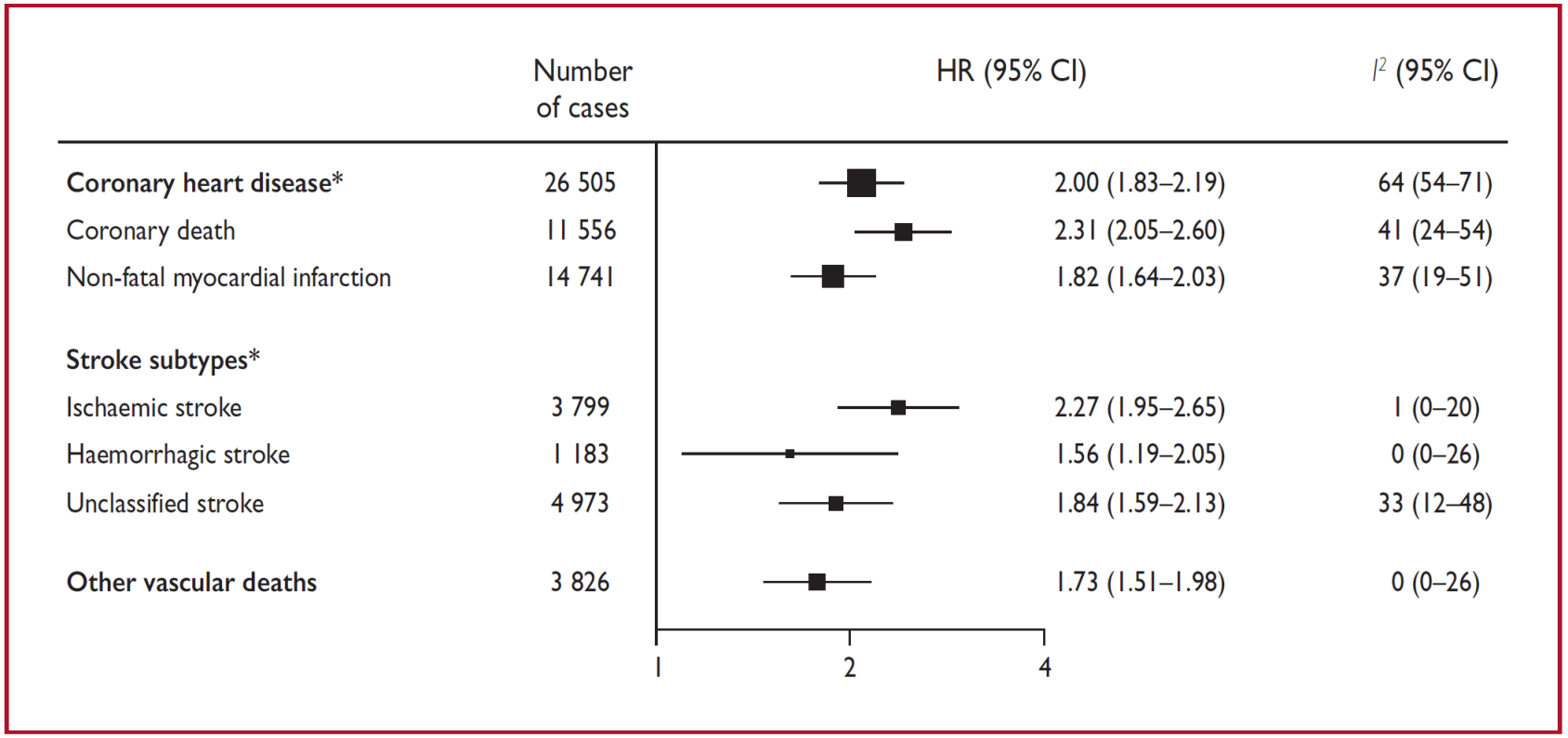
Emerging Risk Factor Collaboration

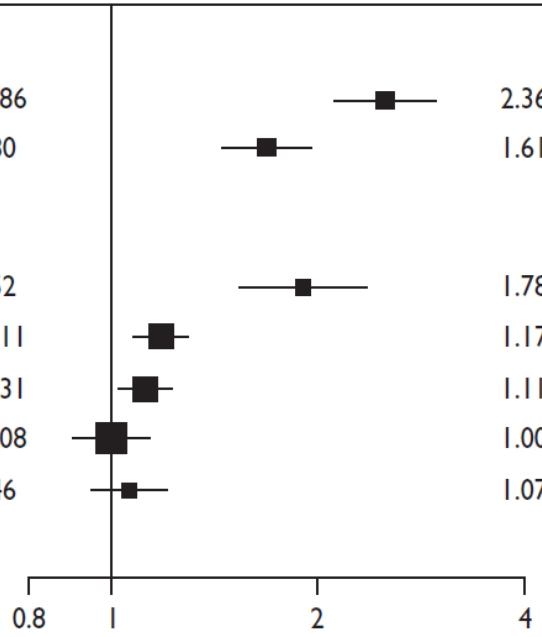
Hazard ratios for vascular outcomes in people with vs. without diabetes mellitus (n=530,083)



Emerging Risk Factor Collaboration

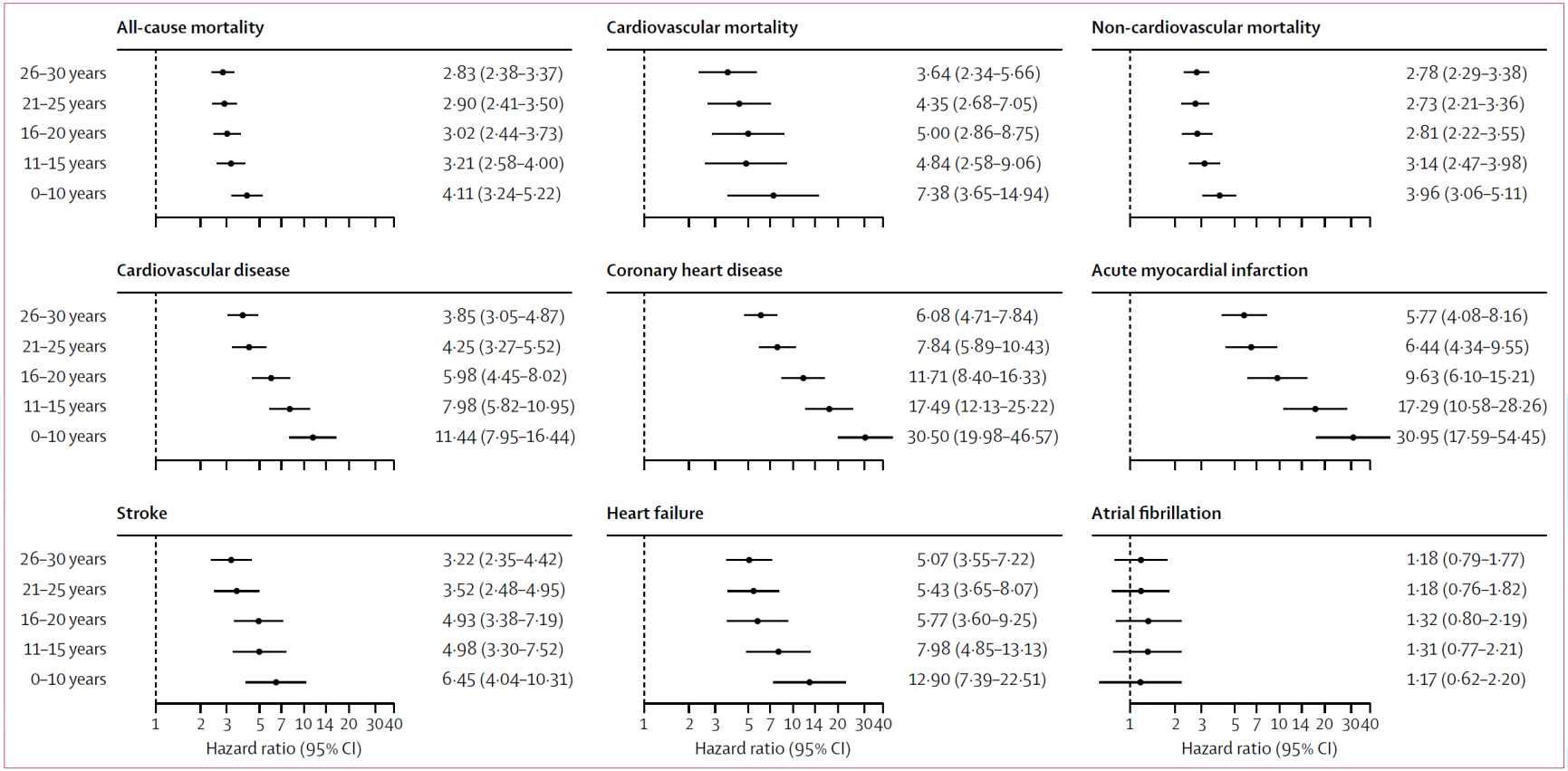
Hazard ratios for coronary heart disease

Fasting blood glucose concentration	Number of participants (%)	Number of cases	HR (95% CI)
Known diabetes at baseline			
≥7 mmol/L	13 122 (4.7%)	1 186	2.36 (2.02–2.76)
<7 mmol/L	5 807 (2.1%)	380	1.61 (1.42–1.82)
No known diabetes at baseline			
≥7 mmol/L	7 240 (2.6%)	452	1.78 (1.56–2.03)
6.1 to <7 mmol/L	19 607 (7.0%)	1 011	1.17 (1.08–1.26)
5.6 to <6.1 mmol/L	32 008 (11.5%)	1 631	1.11 (1.04–1.18)
3.9 to <5.6 mmol/L[a]	185 590 (66.5%)	9 508	1.00 (0.95–1.06)
<3.9 mmol/L	15 916 (5.7%)	646	1.07 (0.97–1.18)



Swedish National Diabetes Register

Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset



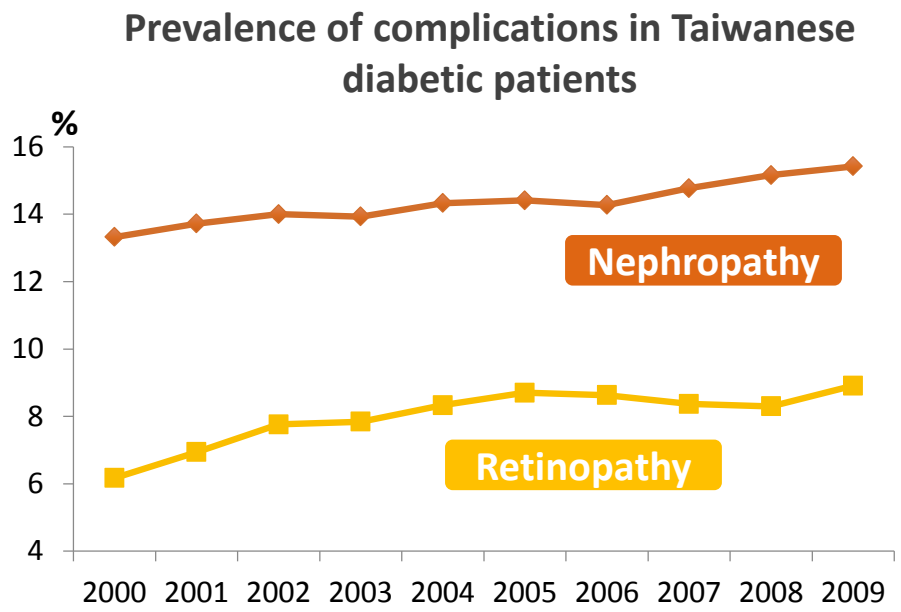
(27 195 individuals with type 1 diabetes and 135 178 matched controls)

Lancet 2018; 392: 477–86.

Diabetes

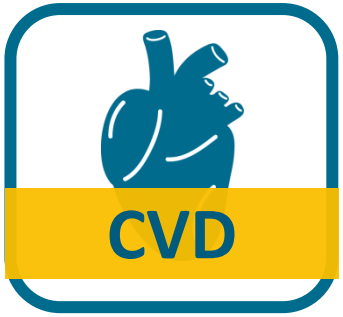
Prevalence of diabetic complications in Taiwan

Microvascular [1]



Significantly increased from 2000 to 2009.[1]

Macrovascular [2]



In 2009, up to 33% of diabetic patients in Taiwan had CVD and 10% of diabetic patients experienced stroke.

CVD: cardiovascular disease.

1. J Formos Med Assoc. 2012;111(11):637-44; 2. J Formos Med Assoc. 2012;111(11):625-36.

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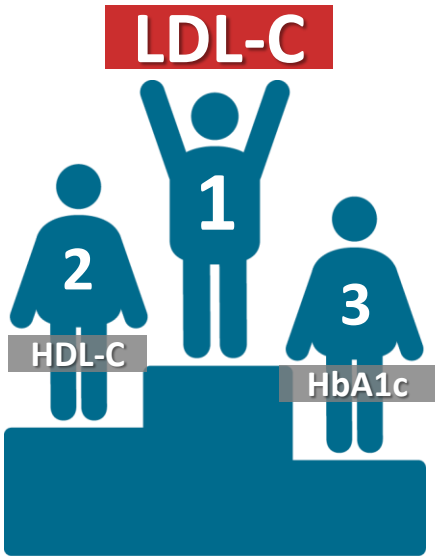
Predictors of CAD risk in DM patients

Stepwise selection of CAD risk factors in 2693 diabetic patients



LDL-C is the most significant risk factor.

Position in model	Coronary artery disease (n=280)	
	Variable	*P* value
First	**Low-density lipoprotein cholesterol**	**< 0.0001**
Second	High-density lipoprotein cholesterol	0.0001
Third	HbA1c	0.0022
Fourth	Systolic blood pressure	0.0065
Fifth	Smoking	0.056

CAD: coronary artery disease; DM: diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; HbA1c: haemoglobin A_{1c}.

BMJ. 1998;316(7134):823-8.

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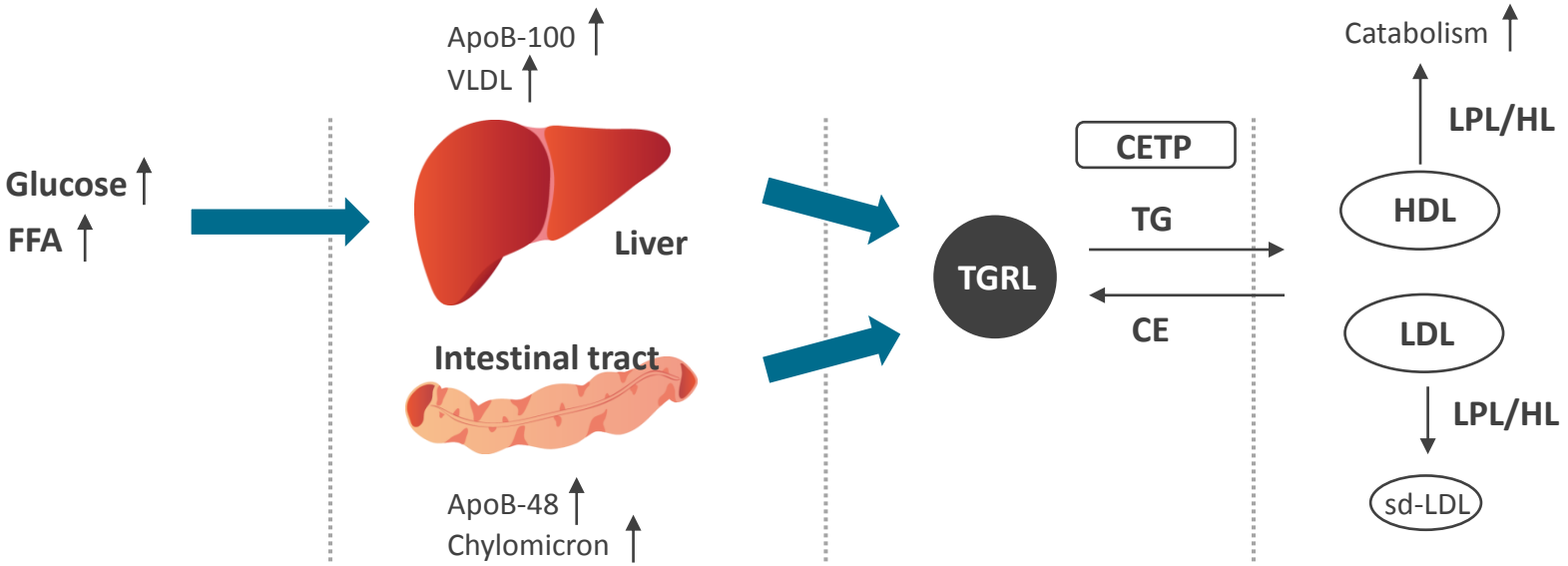
Diabetes

Diabetic dyslipidemia



1 Increased levels of FFA due to defects in insulin action

2 Overproduction of VLDL and chylomicrons

3 Overabundance of TGRL

4 ↓HDL ↑LDL

FFA: free fatty acids; Apo: apolipoprotein; VLDL: very-low density lipoprotein; TGRL: triglyceride-rich lipoprotein; CETP: cholesterol ester transfer protein; TG: triglyceride; CE: cholesteryl ester; HDL: high-density lipoprotein; LPL: lipoprotein lipase; HL: hepatic lipase; LDL: low-density lipoprotein; sd-LDL: small-dense low-density lipoprotein.

Metabolism. 2014;63(12):1469-79.

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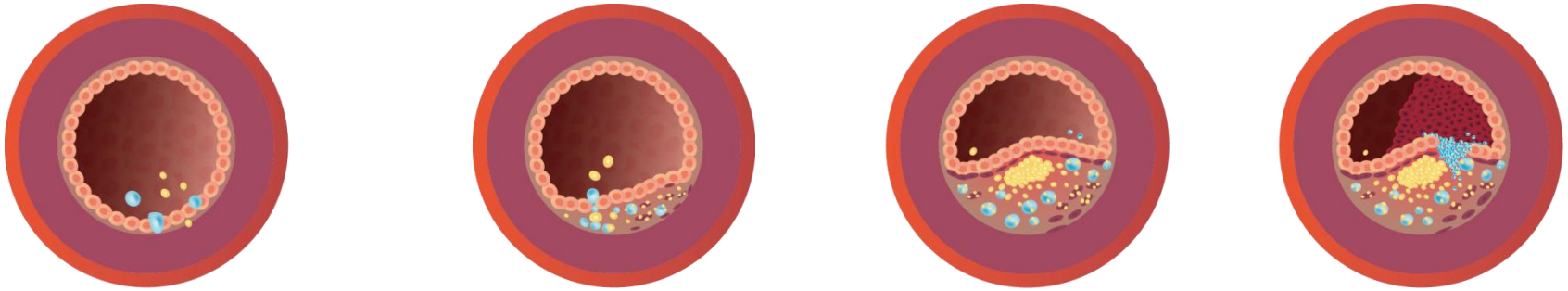
Mechanism of atherosclerosis



1. **Chronic inflammation and injury** in the peripheral or coronary arterial wall
2. **Oxidized LDL particles accumulation** and monocytes infiltration
3. Macrophage-containing **foam cells formation**
4. **Rupture of** atherosclerotic **lesion** leads to acute vascular infarction

LDL: low-density lipoprotein.

Clinical Diabetes. 2008;26(2):77-82.

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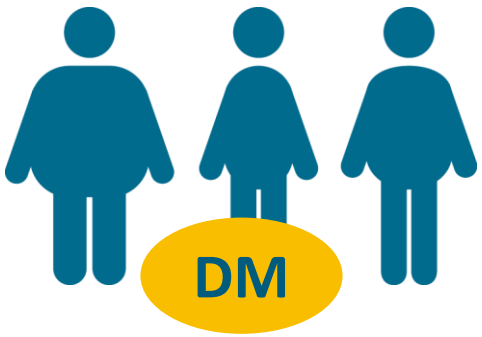
The importance of lipid control in DM patients

Diabetic dyslipidemia might be the main reason of atherosclerosis in diabetic patients [1]



In the Collaborative Atorvastatin Diabetes Study (CARDS) with **2838 diabetic patients** with a mean baseline LDL-C of 117 mg/dL, **atorvastatin significantly reduced major CV events** and the study was terminated earlier due to its favorable result.[2]

DM: diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; CV: cardiovascular.

1. J Clin Endocrinol Metab. 2001;86(3):965-71; 2. Lancet. 2004;364(9435):685-96.

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Diabetes

Guidelines recommended targets for LDL-C

Guidelines	ESC [1] 2016	AACE / ACE [2] 2017	Taiwan Society of Lipids and Atherosclerosis [2] 2017
LDL-C < 55 mg/dL	-	**Extreme risk** • Progressive ASCVD • Established CVD with DM, CKD 3,4 or HeFH	**DM patients with ACS**
LDL-C < 70 mg/dL	**Very high-risk** • Documented CVD • DM with organ damage • GFR < 30 mL/min/1.73 m^2 • SCORE ≥ 10%	**Very high risk** • Established VD • DM or CKD 3,4 with at least 1 risk factor • HeFH	**DM patients with overt CVD**
LDL-C < 100 mg/dL	**High-risk** • Cholesterol > 310 mg/dL • BP ≥ 180/110 mmHg • DM • GFR 30-59 mL/min/1.73 m^2 • SCORE ≥ 5% and < 10%	**High risk** • CHD risk equivalent • ≥ 2 risk factors and 10-year risk > 10% • DM or CKD 3,4 without risk factor	**DM patients without overt CVD**

ESC: European Society of Cardiology; AACE: American Association of Clinical Endocrinologists; ACE: American College of Endocrinology; LDL-C: low-density lipoprotein cholesterol; CVD: cardiovascular disease; DM: diabetes mellitus; GFR: glomerular filtration rate; SCORE: systematic coronary risk estimation; BP: blood pressure; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; HeFH: heterozygous familial hypercholesterolemia; VD: vascular disease; CHD: coronary heart disease; ACS: acute coronary syndrome.

1. Eur Heart J. 2016;37(29):2315-81;
2. Endocr Pract. 2017;23(2):207-38;
3. J Formos Med Assoc. 2017;116(4):217-48.

Diabetes

AACE/ACE lipid goal for T2DM patients

A statement from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) in 2017

Risk category	Risk factors [a]/10-year risk [b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	✓ Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL ✓ Established clinical cardiovascular disease in patients with DM, CKD 3,4, 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 ✓ Diabetes or CKD 3, 4 with 1 or more risk factor(s) ✓ HeFH	< 70	< 100	< 80
High risk	≥ 2 risk factors and 10-year risk > 10% or CHD risk equivalent [c], including diabetes or CKD 3, 4 with no other risk factors	< 100	< 130	< 90
Moderate risk	≥ 2 risk factors and 10-year risk < 10%	< 100	< 130	< 90

[a] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or on hypertensive medication), low HDL-C (< 40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), CKD stage 3,4, evidence of coronary artery calcification and age (men ≥ 45; women ≥ 55 years). Subtract 1 risk factor if the person has high HDL-C.
[b] Framingham risk scoring is applied to determine 10-year risk (10 [EL 4]).
[c] Coronary artery disease risk equivalents include diabetes and clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease).
T2DM: type 2 diabetes; ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; DM: diabetes mellitus; CKD: chronic kidney disease; HeFH: heterozygous familial hypercholesterolemia; ACS: acute coronary syndrome; CHD: coronary heart disease; HDL-C: high-density lipoprotein cholesterol; Apo: apolipoprotein.

Modified from 2017 AACE / ACE Consensus Statement: Endocr Pract. 2017;23(2):207-38.

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Recommended statin intensity for diabetic patients

Diabetes

American Diabetes Association®

Statin intensity for diabetic patients recommended by the American Diabetes Association (ADA) in 2018

Steps to Goal

1. Initiating statin monotherapy
2. Adjusting statin dose until maximally tolerated
3. Considering combination therapy

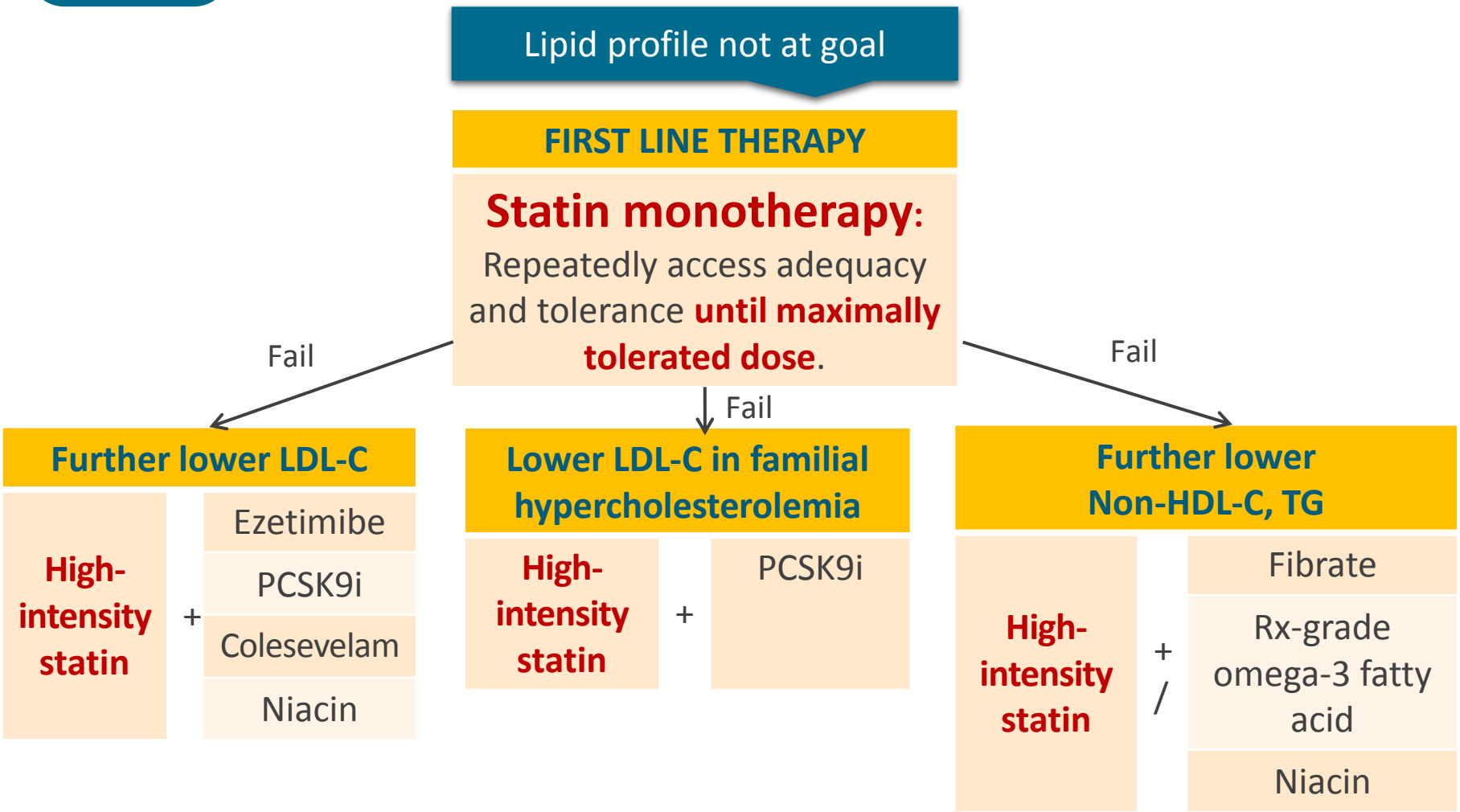
Age	ASCVD	Recommended statin intensity ^ and combination treatment *
< 40 years	No	None †
	Yes	High ➢ If LDL-C ≥ 70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor) #
≥ 40 years	No	Moderate ‡
	Yes	High ➢ If LDL-C ≥ 70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

*In addition to lifestyle therapy.
^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.
†Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL-C ≥ 100 mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.
‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors.
#Adults aged < 40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.
ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; LDL: low-density lipoprotein; PCSK9: proprotein convertase subtilisin/kexin type 9.

Modified from Standards of Medical Care in Diabetes - 2018: Diabetes Care. 2018;41(Suppl 1):S86-S104.

Lipid therapy in diabetic patients

Diabetes



LDL-C: low-density lipoprotein cholesterol; PCSK9 i: proprotein convertase subtilisin/kexin type 9 inhibitor; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

Modified from 2017 AACE / ACE Consensus Statement: Endocr Pract. 2017;23(2):207-38.

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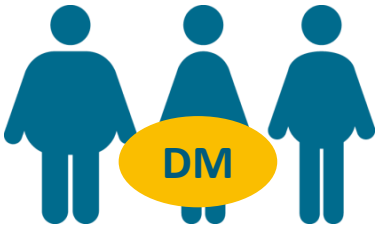
Diabetes

2017 Taiwan lipid guidelines for DM patients



POPULATION

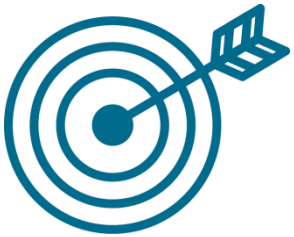
- DM patients with CVD
- DM patients whose age ≥ 40 years
- DM patients whose age < 40 years with CV risk factors

TREATMENT

STATIN

therapy is necessary.

Maximal tolerated statin therapy can be used to reach target.



TARGETS

- LDL-C < 55 mg/dL for DM patients with ACS
- LDL-C < 70 mg/dL for DM patients with overt CVD
- LDL-C < 100 mg/dL for DM patients without CVD

Further TG < 150 mg/dL and HDL-C > 40 mg/dL in men and > 50 mg/dL in women

DM: diabetes mellitus; CVD: cardiovascular disease; CV: cardiovascular; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol.

J Formos Med Assoc. 2017;116(4):217-48.

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Cardiovascular risk categories

Very-high risk (LDLC <55)

2016 European Guidelines on CVD prevention in clinical practice	2019 ESC/EAS Guidelines for management of dyslipidemia
DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.	**DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).**

Cardiovascular risk categories

High risk (LDLC <70)

2016 European Guidelines on CVD prevention in clinical practice	2019 ESC/EAS Guidelines for management of dyslipidemia
Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).	Patients with DM without target organ damage, with DM duration >10 years or another additional risk factor.

Cardiovascular risk categories

Moderate risk (LDLC <100)

2016 European Guidelines on CVD prevention in clinical practice	2019 ESC/EAS Guidelines for management of dyslipidemia
	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors.

2019 ESC lipid guidelines for DM patients

Diabetes

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

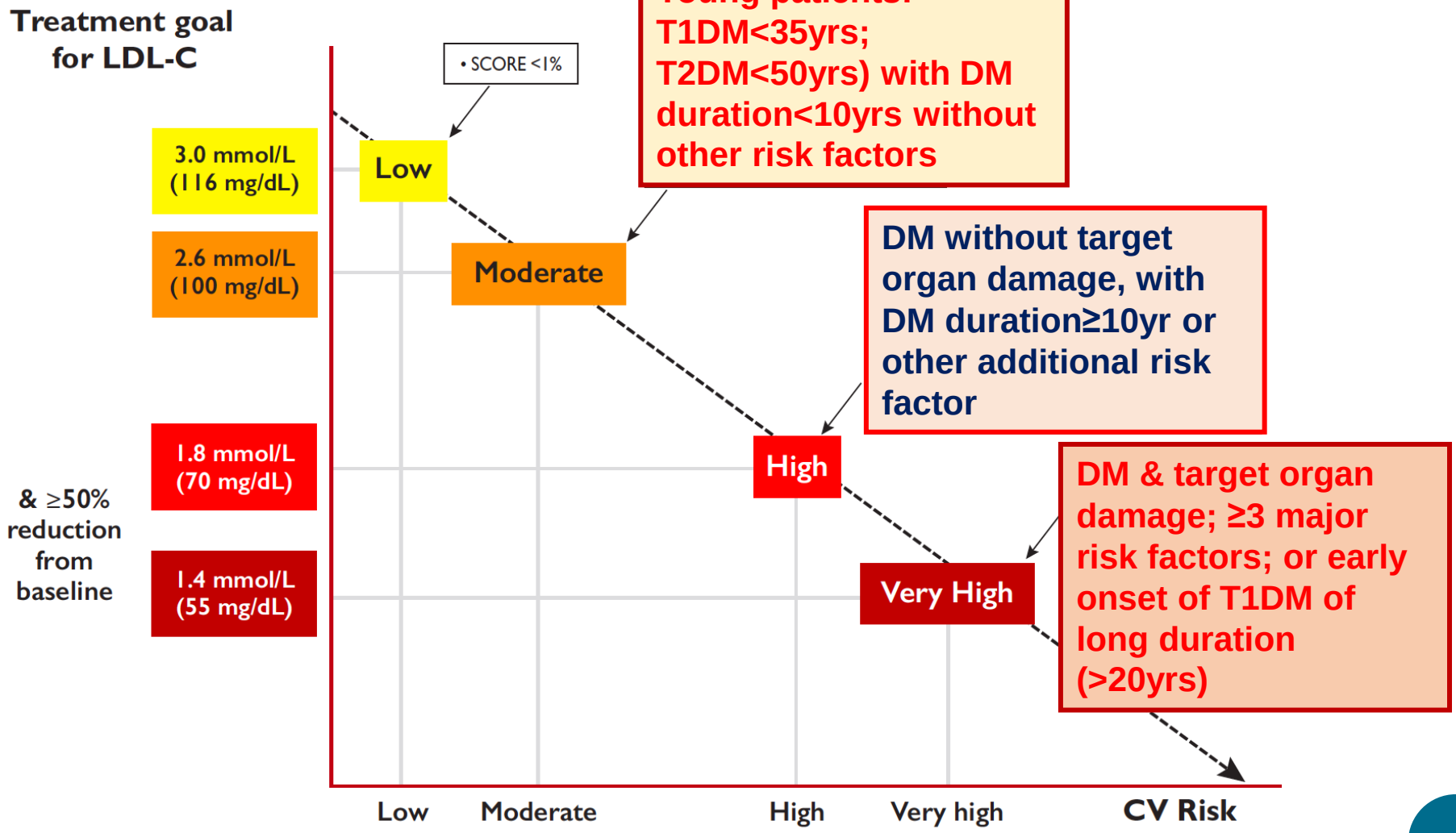
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

2019 ESC lipid guidelines for DM patients

Diabetes



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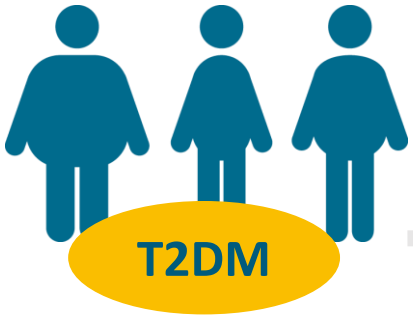
Study design of CARDS

Global



R

Atorvastatin 10 mg daily — 1428

Placebo — 1410

- Stroke
- Nonfatal MI
- Unstable angina
- Resuscitated cardiac arrest
- Cardiovascular-related death
- Revascularization procedures

40 - 75 years;
No prior CVD;
1+ CHD risk factor;
LDL-C ≤ 160 mg/dL;
TG ≤ 600 mg/dL.

Median follow-up of **3.9** years

Intention-to-treat

CARDS: Collaborative Atorvastatin Diabetes Study; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; CHD: coronary heart disease; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; CV: cardiovascular; MI: myocardial infarction.

Lancet. 2004;364(9435):685-96.

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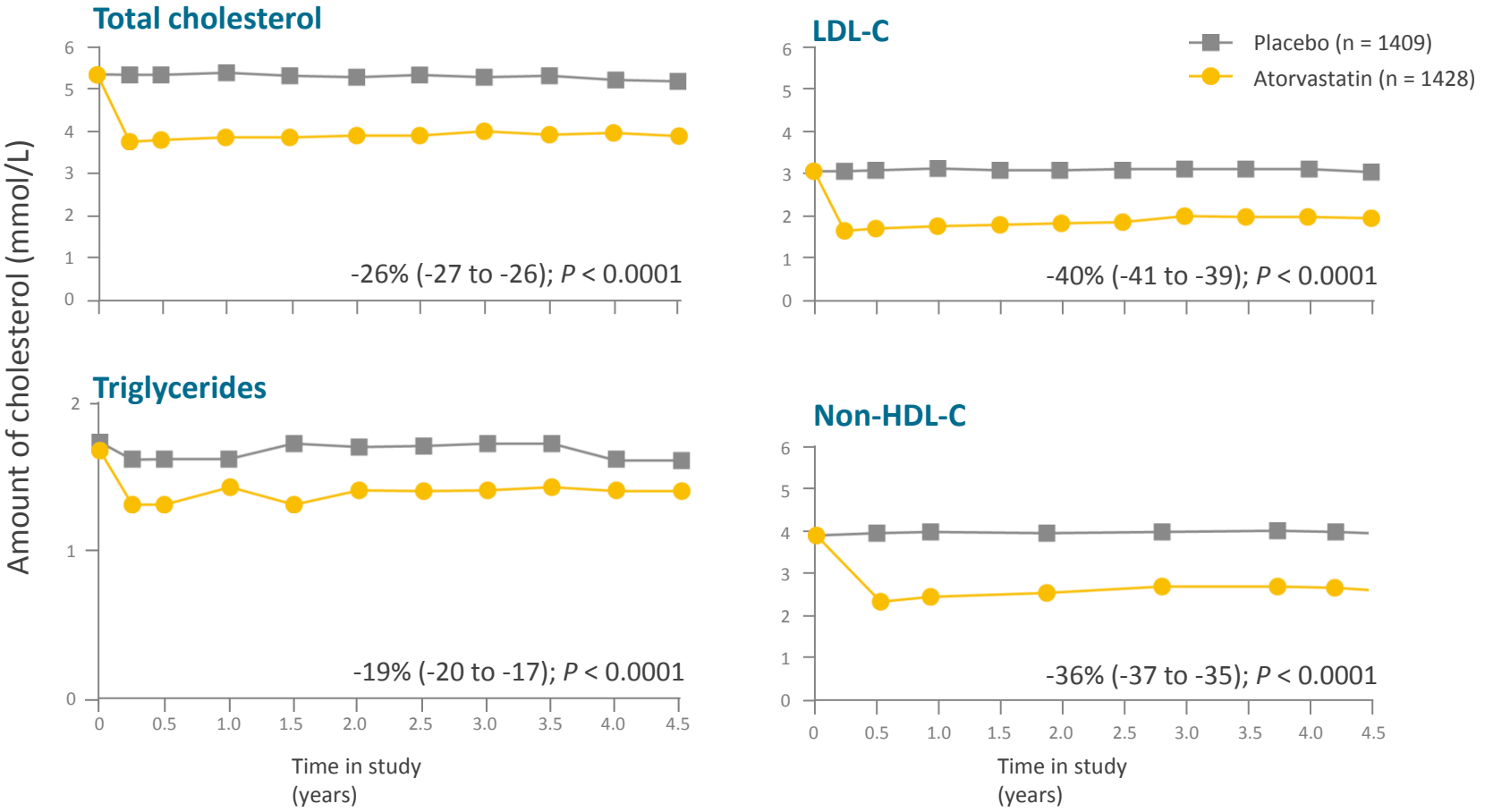
Results of CARDS

Atorvastatin significantly reduced total cholesterol, LDL-C, triglycerides, and non-HDL-C.



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

Lancet. 2004;364(9435):685-96.

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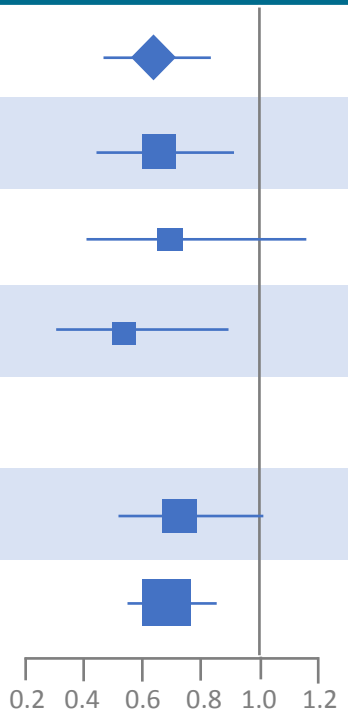
Results of CARDS

CARDS study was stopped 2-year earlier owing to the large and favorable treatment effect of atorvastatin.

	Number of patients with an event (%)		Hazard ratio (95% CI)	*P*
	Placebo (n = 1410)	Atorvastatin 10 mg (n = 1428)		
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



Effect of treatment on primary and secondary endpoints

CI: confidence interval.

Lancet. 2004;364(9435):685-96.

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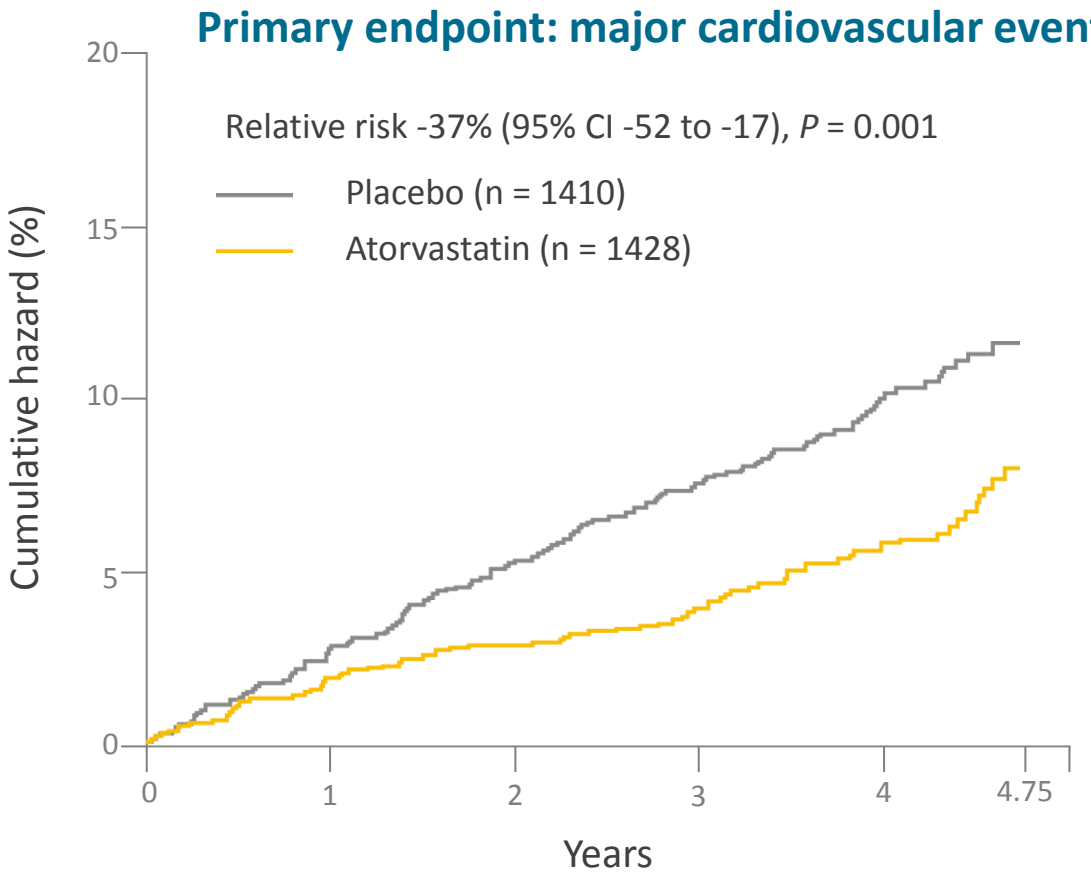
Results of CARDS

Atorvastatin significantly reduced major cardiovascular events by 37% compared with placebo.



CI: confidence interval.

Lancet. 2004;364(9435):685-96.

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Key implications of CARDS

Global

Key implications

1 CV benefit of atorvastatin in DM patients

A 37% of significant reduction in major CV events was reported in atorvastatin-treated DM patients

2 The safety of atorvastatin in DM patients

No excess of AEs was observed in the treatment arm. The AEs-related discontinuation rates were 10% with placebo and 9% with atorvastatin.

CV: cardiovascular; DM: diabetes mellitus; AEs: adverse events.

Lancet. 2004;364(9435):685-96.

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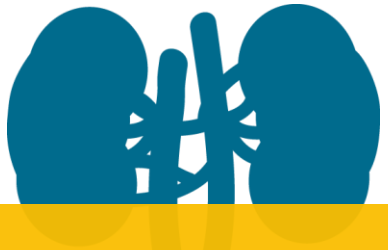
Global

Outcomes of atorvastatin clinical trials

The outcomes of atorvastatin clinical trials in patients with DM focus on:

Major CV events

Inflammatory effects



Renal effects

DM: diabetes mellitus; CV: cardiovascular.

PP-LIP-TWN-0194-201801

Atorvastatin showed CV benefits in DM patients

Significantly reduced cardiovascular events in 4 randomized clinical trials.

Study	CARDS [1] 2004	ASCOT-LLA [2] 2005	TNT [3] 2006	PROVE IT-TIMI 22 [4] 2006
Study design	Double-blind RCT	Subpopulation analysis of double-blind RCTs		
Population	DM patients without high LDL-C level	DM patients with hypertension	DM patients with coronary heart disease	DM patients with acute coronary syndrome
No. of patients	2838	2532 out of 10305	1501 out of 10001	978 out of 4162
Duration	3.9 years	3.3 years	4.9 years	2 years
Intervention	Atorvastatin 10 mg daily (vs placebo)	Atorvastatin 10 mg daily (vs placebo)	Atorvastatin 80 mg daily (vs atorvastatin 10 mg daily)	Atorvastatin 80 mg daily (vs pravastatin 40 mg daily)
Result (compared with comparator)	Reduced major cardiovascular event by 37% (P = 0.001)	Reduced major cardiovascular event or procedure by 23% (P = 0.036)	Reduced major cardiovascular event by 25% (P = 0.026)	Reduced major cardiac event by 25% (P = 0.03)

CV: cardiovascular; DM: diabetes mellitus; RCT: randomized clinical trial; LDL-C: low-density lipoprotein cholesterol.

1. Lancet. 2004;364(9435):685-96; 2. Diabetes Care. 2005;28(5):1151-7;
3. Diabetes Care. 2006;29(6):1220-6; 4. Eur Heart J. 2006;27(19):2323-9.

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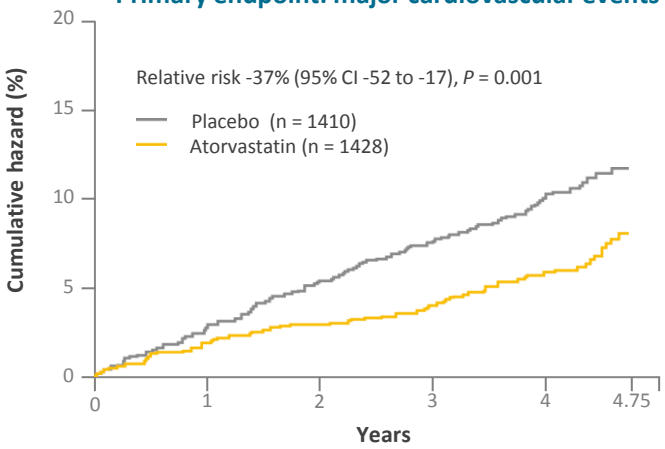
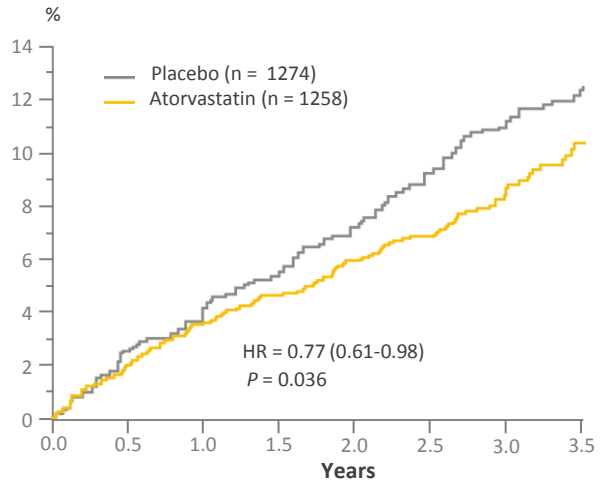
Results of 4 RCTs

Atorvastatin significantly reduced major CV events.

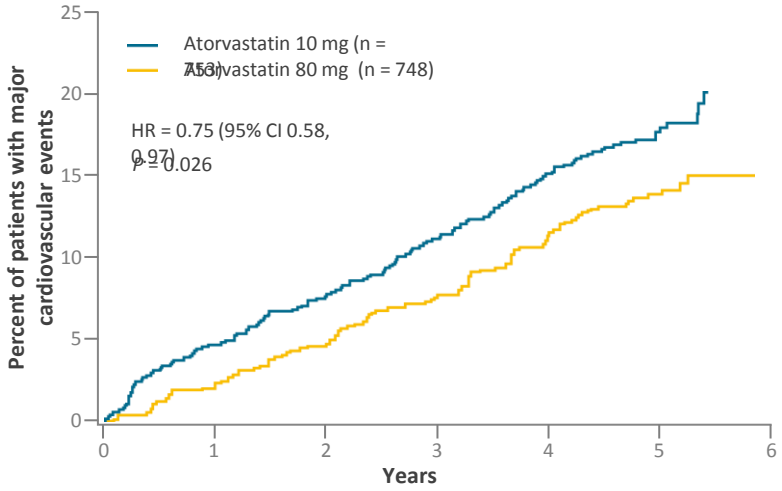
CARDS [1]



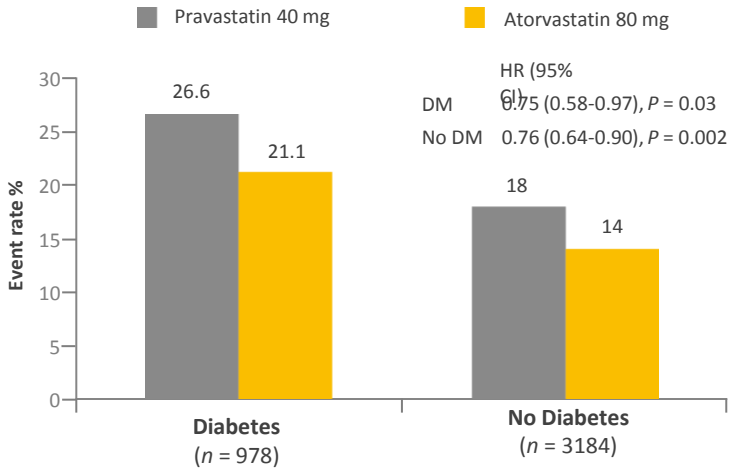
ASCOT-LLA [2]



TNT [3]



PROVE IT –TIMI 22 [4]



RCTs: randomized clinical trials; CV: cardiovascular; HR: hazard ratio; CI: confidence interval.

1. Lancet. 2004;364(9435):685-96; 2. Diabetes Care. 2005;28(5):1151-7;
3. Diabetes Care. 2006;29(6):1220-6; 4. Eur Heart J. 2006;27(19):2323-9.

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Atorvastatin reduced inflammatory markers in DM patients

Significantly reduced vascular inflammatory markers of hsCRP, Lp-PLA2, and OPG in 2 clinical trials.

Study	Davenport et al [1] 2015 (Ireland)	Krebs et al [2] 2016 (Germany)
Study design	Open-label, randomized clinical trial	Double-blind, randomized clinical trial
Population	Male patients with type 2 diabetes and microalbuminuria ceased	Patients with type 1 diabetes
No. of patients	55	28
Duration	1 year	2 years
Intervention	Atorvastatin 80 mg daily (vs atorvastatin 10 mg daily)	Atorvastatin 10 mg daily (vs placebo)
Result (compared with comparator)	Significantly reduced vascular inflammatory markers of hsCRP and OPG at 3 months ($P < 0.001$ and $P < 0.01$; respectively)	Significantly reduced inflammatory marker of Lp-PLA2 ($P < 0.001$)

DM: diabetes mellitus; hsCRP: high sensitivity C-reactive protein; Lp-PLA2: lipoprotein-associated phospholipase A2; OPG: osteoprotegerin.

1. J Diabetes Res. 2015;2015:846807; 2. J Pediatr Endocrinol Metab. 2016;29(10):1181-6.

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Atorvastatin showed renoprotective effects in DM patients

Significantly showed favorable effects on kidney in 3 latest clinical trials.

Study	PLANET I [1] 2015	Shehata et al [2] 2015	Vlad et al [3] 2017
Study design	Double-blind, randomized clinical trial	Double-blind, randomized clinical trial	Randomized pilot trial
Population	DM patients with proteinuria	DM patients with mild-to-moderate chronic kidney disease	Patients with type 2 diabetes
No. of patients	353	130	63
Duration	52 weeks	10 days	6 months
Intervention	Atorvastatin 80 mg daily (vs rosuvastatin 10 mg daily or rosuvastatin 40 mg daily)	Atorvastatin 80 mg daily (vs placebo)	Atorvastatin (vs equipotent dose of rosuvastatin)
Result (compared with comparator)	Significantly reduced urine protein:creatinine ratio. ($P = 0.033$)	Significantly reduced incidence of contrast-induced nephropathy. ($P < 0.05$)	Significantly reduced urinary podocytes and biomarkers of proximal tubule dysfunction. ($P < 0.05$)

DM: diabetes mellitus.

1. Lancet Diabetes Endocrinol. 2015;3(3):181-90; 2. Cardiovasc Ther. 2015;33(2):35-41; 3. Ren Fail. 2017;39(1):112-9.

PP-LIP-TWN-0194-201801

1

Diabetes

Introduction of diabetes and **diabetic dyslipidemia**.

2

Global

Global: Statin trials in diabetic patients.

3

Asia - Taiwan

Asia and Taiwan: Statin trials in diabetic patients.

4

Safety

Safety of statin in diabetic patients.

Clinical trials of atorvastatin in Asia and Taiwan

Atorvastatin trials in Chinese population

Study	Chang et al [1] 2013 (Taiwan)	PAPAGO-T [2] 2013 (Taiwan)	Liu et al [3] 2016 (China)
Study design	Open-label, randomized clinical trial	Double-blind, randomized clinical trial	Randomized clinical trial
Population	T2DM patients with hyperlipidemia	Diabetic patients with hypercholesterolemia	T2DM patients with ACS who underwent PCI
No. of patients	157	125 out of 225	591
Duration	12 weeks	12 weeks	1 year
Intervention	Atorvastatin 40 mg daily (vs atorvastatin 20 mg daily or atorvastatin 10 mg daily)	Atorvastatin 10 mg daily (vs pitavastatin 2 mg daily)	Atorvastatin 40 mg daily (vs atorvastatin 20 mg daily)
Result (compared with comparator)	Significantly increased LDL-C goal attainment ($P < 0.001$)	Significantly reduced LDL-C and others lipid variables in both treatment group. (P not shown)	Significantly reduced major adverse cardiovascular event by 42.5% ($P = 0.018$)

T2DM: type 2 diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention.

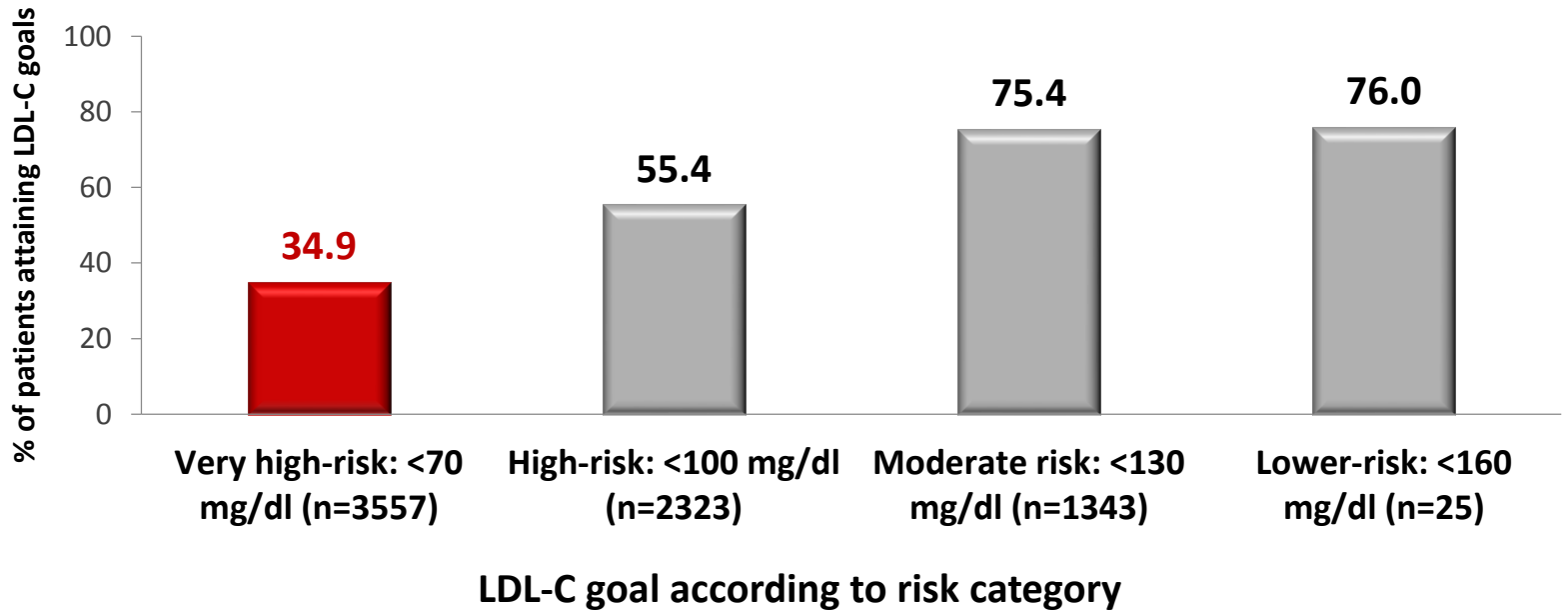
1. Tzu Chi Medical Journal. 2013;25(3):168-74; 2. PLoS One. 2013;8(10):e76298; 3. Int J Cardiol. 2016;222:22-6.

PP-LIP-TWN-0194-201801

Low LDL-C target attainment rate in Asia

According to the CEPHEUS Pan-Asian survey conducted in eight Asian countries, the LDL-C goal attainment rates were 49.1% in the overall population (n = 7279) and 49.5% in Taiwan (n = 999).

Only 34.9% of very high risk patients achieved their LDL-C goal.



LDL-C: low-density lipoprotein cholesterol.

Eur J Prev Cardiol. 2012;19(4):781-94.

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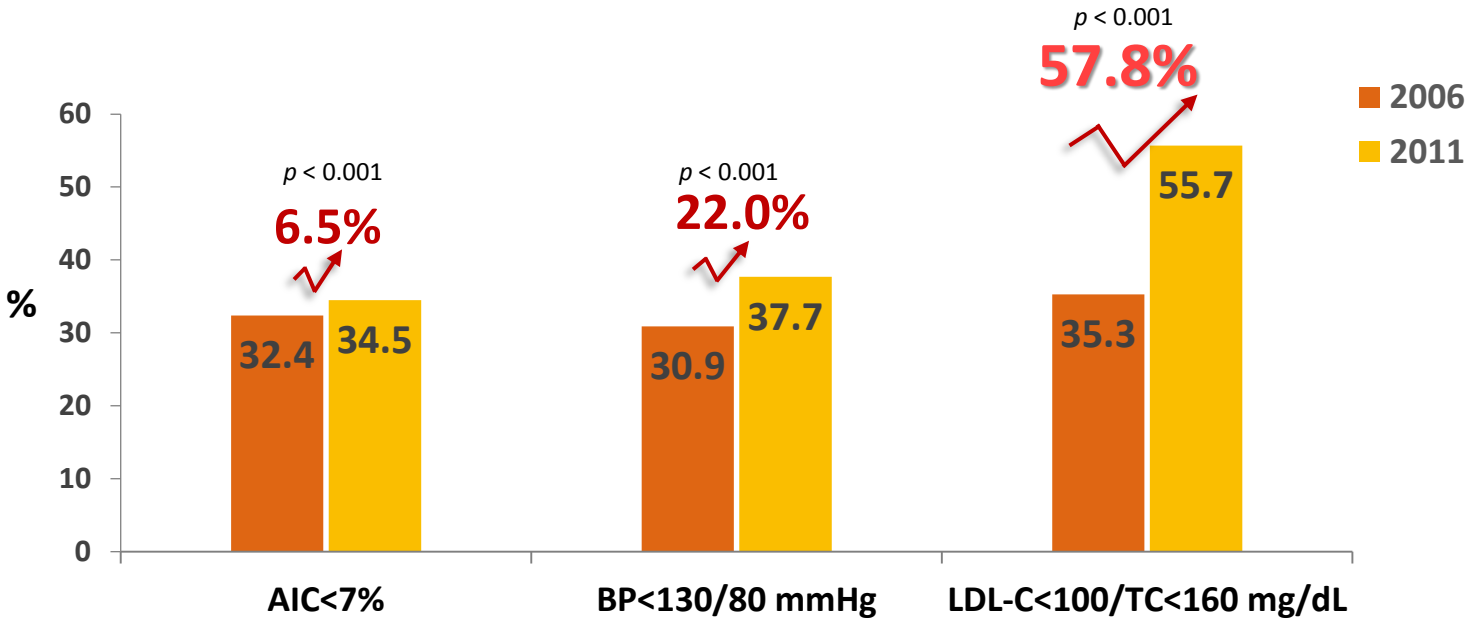
Low LDL-C target attainment rate in Taiwan

Lipid attainment rate increased by 57.8% from 2006 to 2011 in Taiwan. However, up to 44.3% of diabetic patients still failed to achieve lipid goal in 2011.

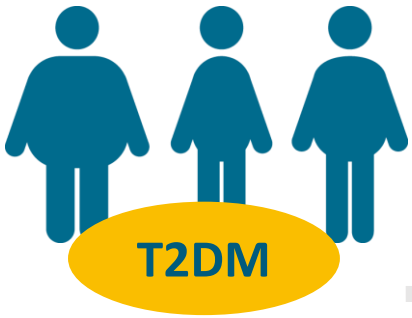


Attainment rates of all diabetic patients in 2006 (n = 7541) and 2011 (n = 5599).

LDL-C: low-density lipoprotein cholesterol; BP: blood pressure; TC: triglyceride.

Diabetes Res Clin Pract. 2013;99(2):112-9.

Study design of atorvastatin trial in Taiwan



18-80 years;
Hyperlipidemia;
LDL-C ≤ 130 mg/dL;
TG < 400 mg/dL;
HbA1c ≤ 10%.

R

Atorvastatin 40 mg daily	53
Atorvastatin 20 mg daily	52
Atorvastatin 10 mg daily	52

Goal attainment rate

Percent change from baseline to week 12

12-week of follow-up

T2DM: type 2 diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HbA1c: haemoglobin A_{1c}.

Tzu Chi Medical Journal. 2013;25(3):168-74.

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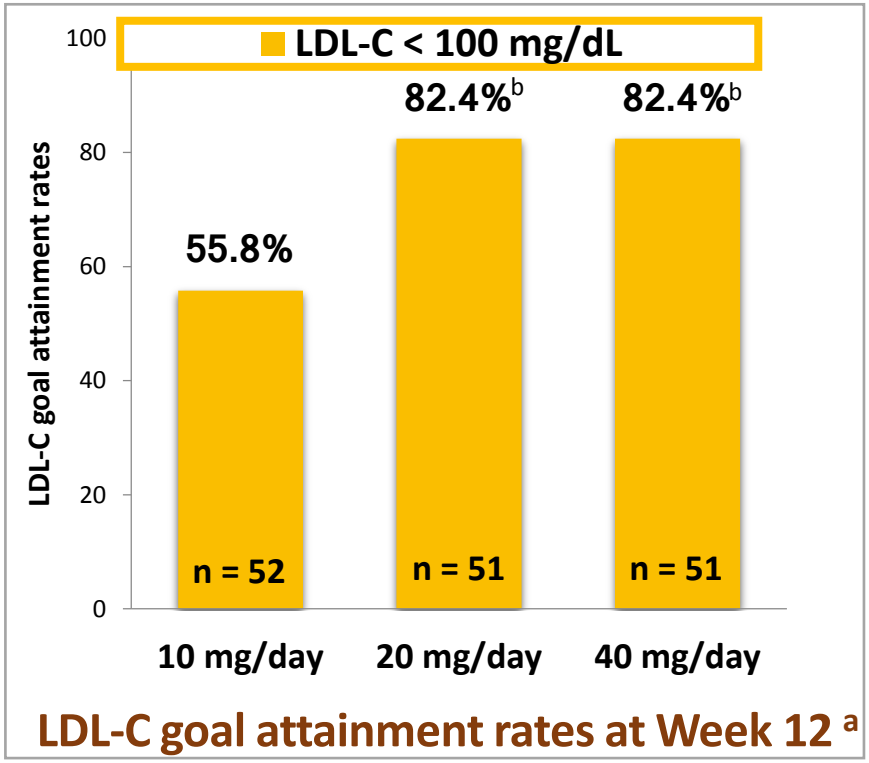
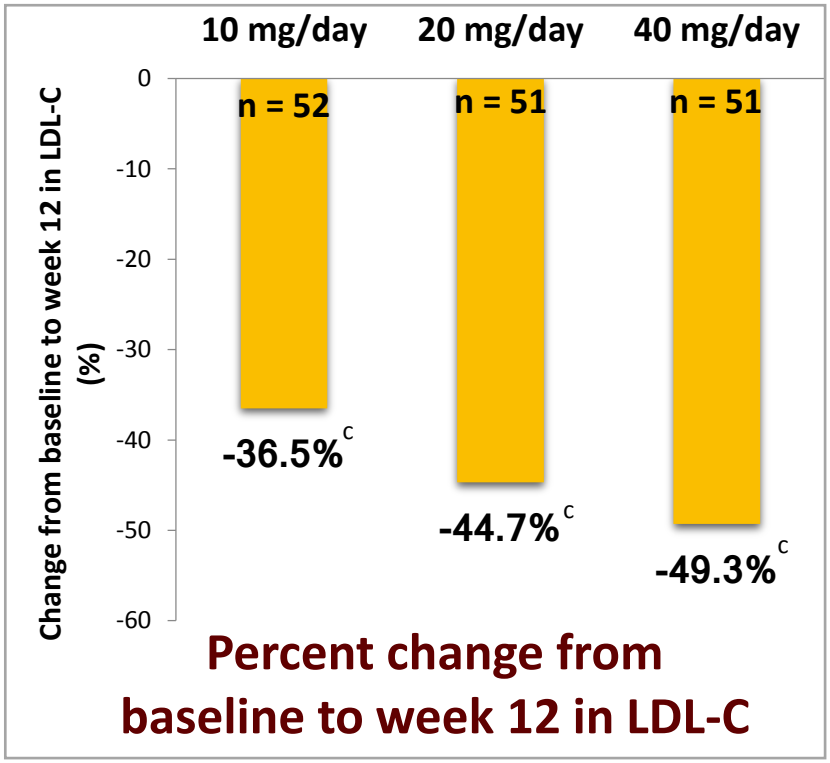
Results of Taiwan trial

LDL-C goal attainment rates significantly increased as the dose of atorvastatin increased. A significant and similar trend was also observed in percent change in LDL-C.



LDL-C goal attainment rates at Week 12 [a]



Percent change from baseline to week 12 in LDL-C

[a] Indicates the response significantly increased as the dose increased; [b] Indicates a significant difference ($p < 0.001$) compared to the 10 mg/day group; [c] Changes are significant compared to baseline.

LDL-C: low-density lipoprotein cholesterol.

Tzu Chi Medical Journal. 2013;25(3):168-74.

PP-LIP-TWN-0194-201801

Key implications of Taiwan trial

Key implications

1 Higher dose, higher goal attainment rate

A further 4% reduction in LDL-C was achieved for every 10 mg of atorvastatin dose up-titration.

2 The safety of atorvastatin in Taiwan

Treatment-related adverse events were mild and infrequent. (21.2% for atorvastatin 10 mg daily, 15.7% for atorvastatin 20 mg daily, and 25% for atorvastatin 40 mg daily)

3 Some limitations of this study

Short study duration (12 weeks); use of surrogate endpoints.

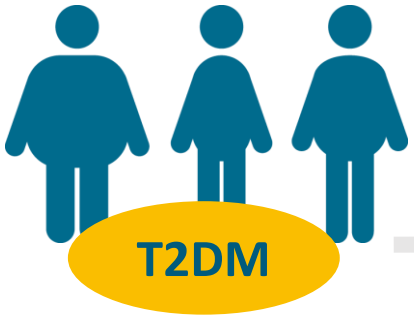
LDL-C: low-density lipoprotein cholesterol.

Tzu Chi Medical Journal. 2013;25(3):168-74.

PP-LIP-TWN-0194-201801

Study design of atorvastatin trial in China

Major adverse cardiovascular events



≤ 80 years;
With ACS;
Underwent PCI.

R

Atorvastatin 40 mg daily — 297

Atorvastatin 20 mg daily — 294

Cardiovascular death
Spontaneous MI
Unplanned revascularization

1-year of follow-up

T2DM: type 2 diabetes mellitus; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; MACE: major adverse cardiovascular events; MI: myocardial infarction.

Int J Cardiol. 2016;222:22-6.

PP-LIP-TWN-0194-201801

Baseline characteristics of patients

Variable	High intensity (n = 297)	Moderate intensity (n = 294)	*P* value
Male, n (%)	143 (48.2)	148 (50.3)	0.59
Age, years	61.6 ± 8.7	62.1 ± 10.2	0.33
BMI, kg/m^2	28.4 ± 3.9	27.6 ± 4.5	0.12
STEMI, n (%)	146 (49.2)	144 (49.0)	0.97
NSTEMI, n (%)	67 (22.6)	72 (24.5)	0.58
Hypertension, n (%)	196 (66.0)	208 (70.8)	0.21
Current smokers, n (%)	63 (21.2)	58 (19.7)	0.65
Previous MI, n (%)	36 (12.1)	43 (14.6)	0.37
Previous PCI, n (%)	53 (17.9)	57 (19.4)	0.63
Previous CABG, n (%)	9 (3.0)	11 (3.7)	0.63
Previous stroke, n (%)	41 (13.8)	37 (12.6)	0.66
EF, (%)	61.7 ± 9.4	59.6 ± 10.1	0.22
Aspirin, n (%)	286 (96.3)	289 (98.3)	0.13
Clopidogrel, n (%)	281 (94.6)	281 (95.6)	0.59
ACEi/ARB, n (%)	274 (92.3)	271 (92.2)	0.97
β-blocker, n (%)	253 (85.2)	258 (87.8)	0.36
ALT, IU/L	25.8 ± 12.4	27.3 ± 13.6	0.11
CRE, umol/L	72.4 ± 24.0	77.9 ± 28.6	0.14
hsCRP, mg/L	4.1 ± 2.3	4.3 ± 2.4	0.32
LDL-C, mmol/L	3.2 ± 0.9	3.1 ± 0.7	0.47
HDL-C, mmol/L	1.1 ± 0.3	1.2 ± 0.5	0.26
TG, mmol/L	1.8 ± 0.9	1.7 ± 1.1	0.29
Haemoglobin A_{1c}, %	7.2 ± 0.9	7.1 ± 1.0	0.38

BMI: body mass index; STEMI: ST-segment elevation myocardial infarction; NSTEMI: NON ST-segment elevation myocardial infarction; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; EF: ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ALT: alanine aminotransferase; CRE: creatinine; hsCRP: high sensitive C-reactive protein; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

Nearly 50% of male

Mean age of 62 years

More than 85% of them received aspirin, clopidogrel, ACEi/ARB, and β-blocker

Mean LDL-C of 3.2 and 3.1 mmol/L, respectively

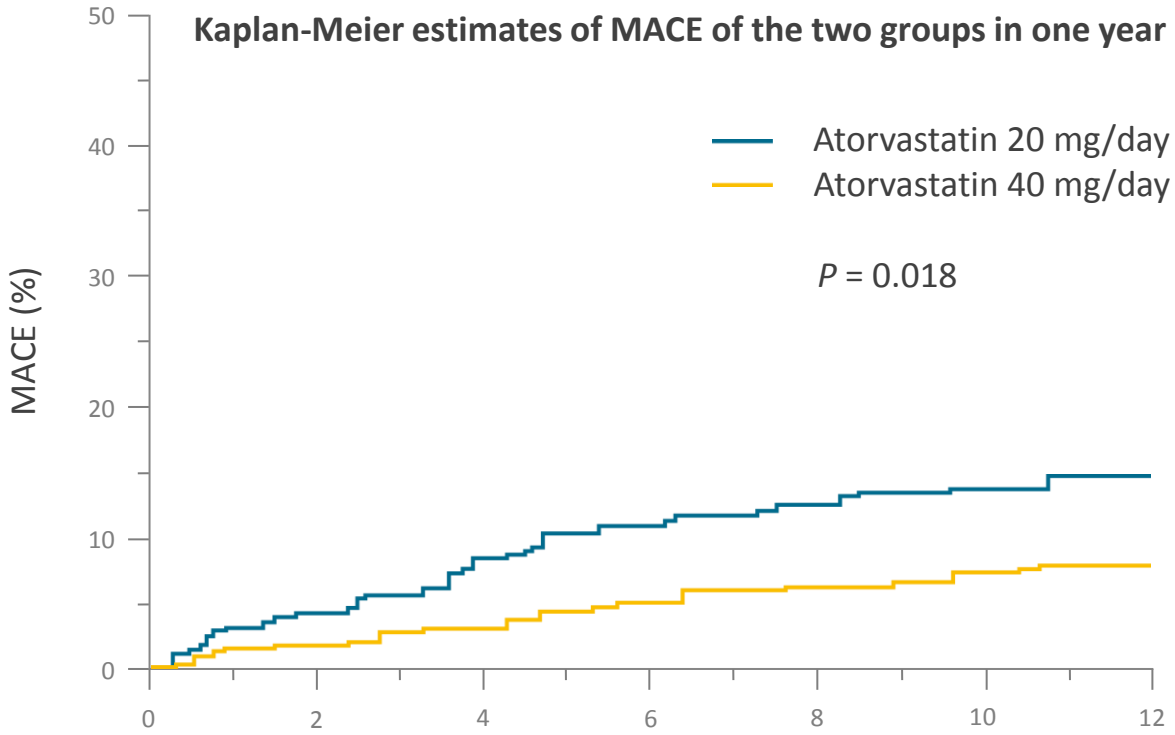
Mean HbA1c of 7.2% and 7.1%, respectively

Int J Cardiol. 2016;222:22-6.

PP-LIP-TWN-0194-201801

Survival curve of MACE

Atorvastatin 40 mg daily significantly reduced MACE by 42.5% in comparison to atorvastatin 20 mg daily.



Atorvastatin							
20 mg/day	286	274	263	253	249	245	243
40 mg/day	286	280	276	270	267	264	261

MACE: major adverse cardiovascular events.

Int J Cardiol. 2016;222:22-6.

PP-LIP-TWN-0194-201801

Key implications of China trial

Key implications

1 CV benefit of high intensity atorvastatin

A 42.5% of significant reduction in MACE was reported in the high intensity group (40 mg daily) compared with the moderate intensity group (20 mg daily).

2 The safety of atorvastatin in Chinese patients

No significant differences of incidence of myalgia and ALT elevation between two groups. (1.0% vs. 0.7%, *P* = 0.66; 7.4% vs. 4.8%, *P* = 0.18; high vs. moderate intensity, respectively)

3 Atorvastatin use in secondary prevention

This study enrolled DM patients who had ACS and underwent PCI.

CV: cardiovascular; MACE: major adverse cardiovascular events; ALT: alanine aminotransferase; DM: diabetes mellitus; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention.

Int J Cardiol. 2016;222:22-6.

PP-LIP-TWN-0194-201801

Study design of atorvastatin trial in Asia

18-80 years;
160 mg/dL < LDL-C < 250 mg/dL;
Triglycerides < 400 mg/dL.

R

79 → Atorvastatin 10 mg daily → Atorvastatin 20 mg daily

78 → Simvastatin 10 mg daily → Simvastatin 20 mg daily

6-week of diet/placebo run-in

8-week of 10 mg statins therapy

8-week of 20 mg statins therapy

Eight medical centers in six Asian countries or areas (Taiwan, Philippines, Thailand, Singapore, Indonesia, and Hong Kong) enrolled patients in this study.

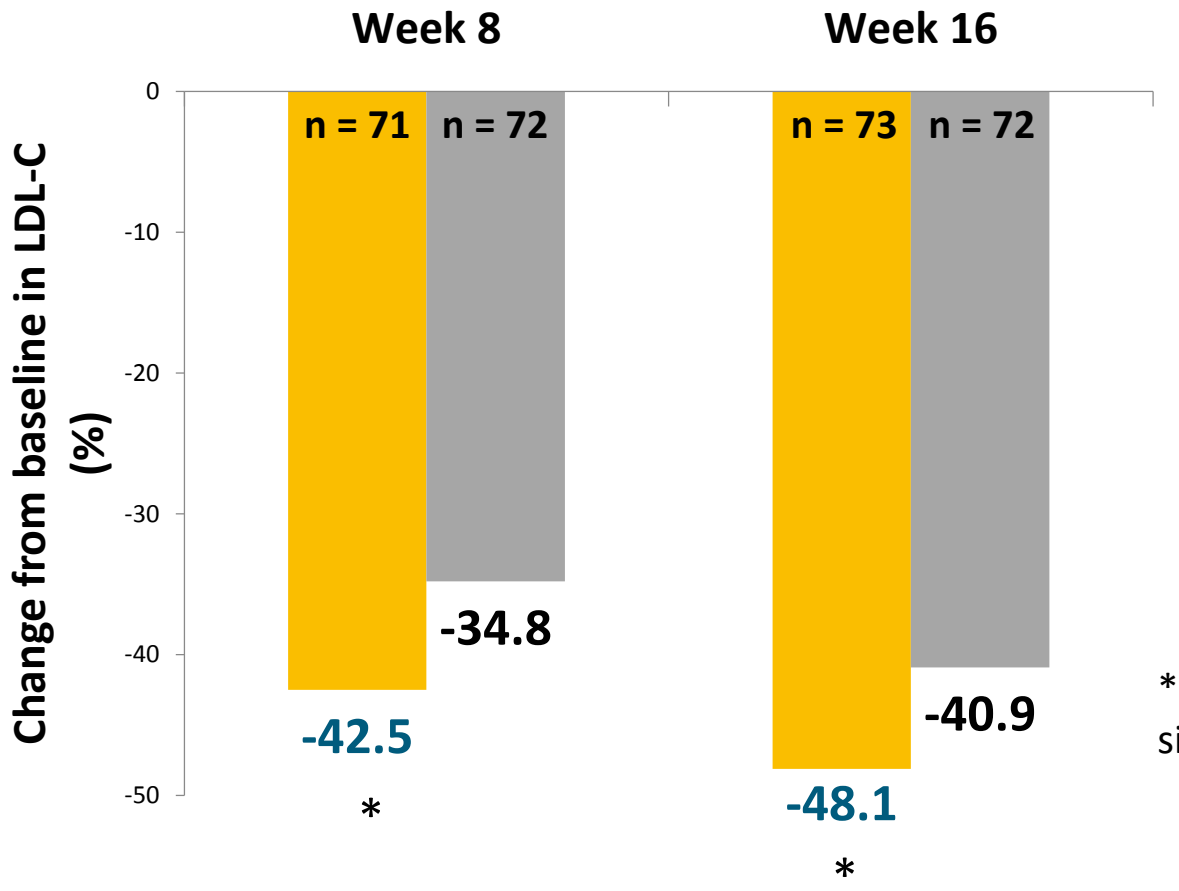
J Formos Med Assoc. 2002;101(7):478-87.

LDL-C: low-density lipoprotein cholesterol.

PP-LIP-TWN-0194-201801

Efficacy outcomes in Asian trial

Atorvastatin had a significantly greater reduction in LDL-C at week 8 and week 16, compared with simvastatin.



* $P < 0.01$ compared with simvastatin.

LDL-C: low-density lipoprotein cholesterol.

J Formos Med Assoc. 2002;101(7):478-87.

Safety outcomes in Asian trial

No significant differences in adverse events between atorvastatin group and simvastatin group.

Body system/Adverse event	Adverse events	
	Atorvastatin (n = 76)	Simvastatin (n = 75)
Any adverse event	**21 (28%)**	**21 (28%)**
Body as a whole	8 (11%)	10 (13%)
Infection	2 (3%)	5 (7%)
Malaise	4 (5%)	1 (1%)
Chest pain	0 (0%)	3 (4%)
Cardiovascular	6 (8%)	5 (7%)
Hypertension	4 (5%)	1 (1%)
Digestive	6 (8%)	3 (4%)
Constipation	4 (5%)	1 (1%)
Metabolic/ nutritional	3 (4%)	0 (0%)
Nervous	6 (8%)	5 (7%)
Dizziness	5 (7%)	2 (3%)
Respiratory	1 (1%)	2 (3%)
Skin and appendages	4 (5%)	3 (4%)
Rash	2 (3%)	2 (3%)
Special senses	3 (4%)	2 (3%)

28% of adverse events in both groups

J Formos Med Assoc. 2002;101(7):478-87.

Key implications of Asian trial

Asia - Taiwan

Key implications

1 Efficacy outcomes

More LDL-C reduction with atorvastatin 10/20 mg in comparison with simvastatin 10/20 mg.

2 Safety outcomes

No significant differences in adverse events between two groups.

J Formos Med Assoc. 2002;101(7):478-87.

PP-LIP-TWN-0194-201801

1

Diabetes

Introduction of diabetes and **diabetic dyslipidemia**.

2

Global

Global:
Statin trials in diabetic patients.

3

Asia - Taiwan

Asia and Taiwan:
Statin trials in diabetic patients.

4

Safety

Safety of statin in diabetic patients.

PP-LIP-TWN-0194-201801

Study population

58 out of 101 **atorvastatin randomized clinical trials** enrolled ≥ 1 Asian patient(s)

January 01, 1992 - March 30, 2012

6 long-term trials with CV outcomes (Total: n = 39172; **Asian: n = 547**)

Median duration of 3.1-4.9 years

- Asian patients receiving placebo or others (n = 203)
- Asian patients receiving **atorvastatin** (**n = 344**)

52 short-term trials (Total: n = 38780; **Asian: n = 2644**)

Median duration of 4-72 weeks

- Asian patients receiving **atorvastatin** (**n = 2175**)
- Asian patients receiving placebo or others (n = 469)

CV: cardiovascular.

In total, 3191 Asian patients were identified, of whom 2519 received atorvastatin.

Cardiovasc Ther. 2016;34(6):431-40.

Baseline of patients

Safety findings for Asian patients in long- and short-term trials of atorvastatin

	AEs	SAEs	Treatment-related AEs/SAEs leading to discontinuation
Pooled long-term trials			
ATV 10 mg	214 (89.9)	61 (25.6)	11 (4.6)*
ATV 80 mg	101 (95.3)	35 (33.0)	13 (12.3)*
Placebo	170 (91.4)	46 (24.7)	10 (5.4)
Pooled short-term trials			
ATV all doses	755 (34.7)	69 (3.2)	43 (2.0)
ATV 10 mg	263 (28.2)	22 (2.4)	17 (1.8)
ATV 20 mg	88 (30.5)	2 (0.7)	5 (1.7)
ATV 40 mg	324 (41.6)	36 (4.6)	13 (1.7)
ATV 80 mg	80 (45.7)	9 (5.1)	8 (4.6)
Placebo	65 (57.0)	10 (8.8)	3 (2.6)
Other statins	97 (35.1)	11 (4.0)	5 (1.8)
Other treatments	12 (15.2)	0 (0)	1 (1.3)

* $P < 0.05$ versus other atorvastatin dose.

Long-term trials

No significant differences in the incidences of AEs, SAEs, and treatment-related AEs/SAEs discontinuations across groups were observed, except for the treatment-related AEs/SAEs discontinuations between ATV 80 mg and ATV 10 mg.

Short-term trials

No significant differences in the incidences of AEs, SAEs, and treatment-related AEs/SAEs discontinuations across groups were observed.

AEs: adverse events; ATV: atorvastatin; SAEs: serious adverse events.

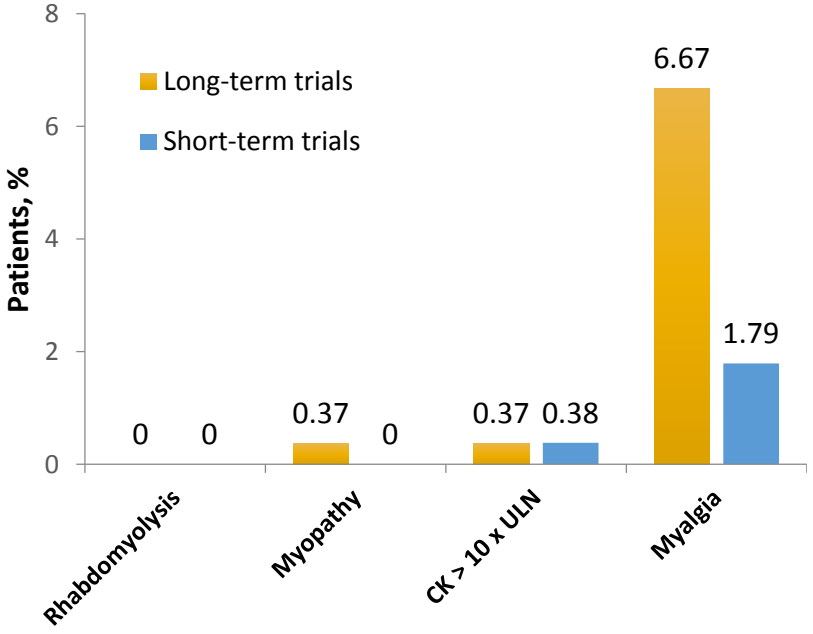
Cardiovasc Ther. 2016;34(6):431-40.

PP-LIP-TWN-0194-201801

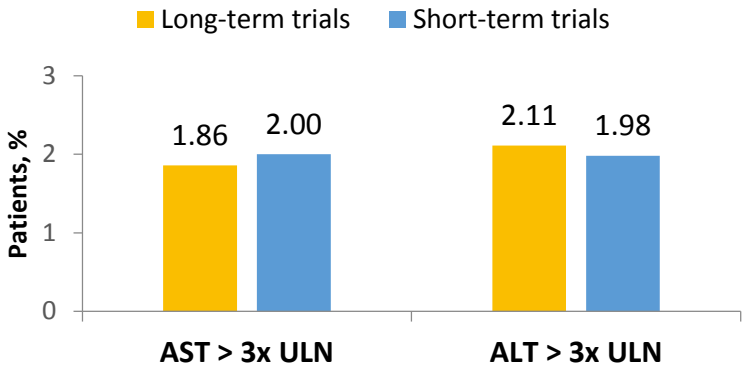
Survival curve of MACE

No cases of rhabdomyolysis were reported and most of the rates of musculoskeletal, hepatic or renal AEs were lower than 2%.

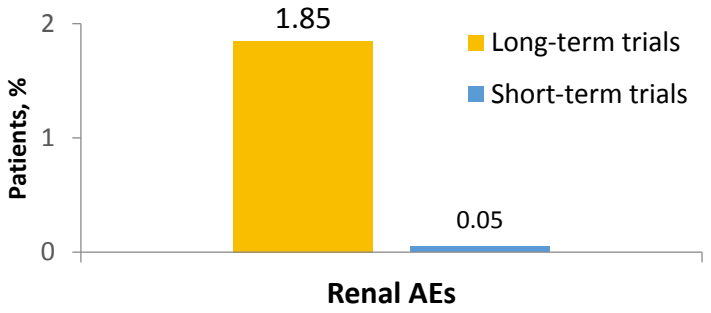
Musculoskeletal safety



Hepatic safety



Renal safety



MACE: major adverse cardiovascular events; AEs: adverse events; CK: creatine kinase; ULN: upper limit of normal; AST: aspartate transaminase; ALT: alanine transaminase.

Cardiovasc Ther. 2016;34(6):431-40.

PP-LIP-TWN-0194-201801

Key implications in Asian patients

Safety

Key implications

1 The safety of atorvastatin 10-40 mg daily

All rates of AEs and SAEs were low and comparable to placebo.

2 The safety of atorvastatin 80 mg daily

All rates of AEs and SAEs were similar to placebo. Data regarding AEs-related discontinuations needs further investigation due to the relatively small sample size.

3 Musculoskeletal, hepatic, and renal safety

All rates of musculoskeletal, hepatic, and renal AEs were 2% or lower than 2%, except for myalgia in pooled long-term trials (6.7%).

AEs: adverse events; SAEs: serious adverse events.

Cardiovasc Ther. 2016;34(6):431-40.

PP-LIP-TWN-0194-201801

Safety profile of atorvastatin in DM patients

No significant differences of treatment-related AEs between groups were observed in two atorvastatin clinical trials conducted in DM patients.

CARDS [1] Median duration of 3.9 years (n = 2838)		
	Atorvastatin 10 mg/day (n = 1428)	**Placebo** (n = 1410)
Treatment-related		
AEs, %	23.0	25.4
Serious AEs, %	1.1	1.1
AEs-related discontinuations, %	2.9	3.4

Subgroup analysis of TNT [2] Median duration of 4.9 years (n = 1501)		
	Atorvastatin 80 mg/day (n = 748)	**Atorvastatin 10 mg/day** (n = 753)
Treatment-related		
AEs, %	7.0	5.4

DM: diabetes mellitus; AEs: adverse events.

1. Diab Vasc Dis Res. 2008;5(3):177-83; 2. Diabetes Care. 2006;29(6):1220-6.

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Safety

Safety profile of atorvastatin in DM patients

In CARDS and TNT trials, safety outcomes focus on:

DM: diabetes mellitus; LDL-C: low-density lipoprotein cholesterol.

Diab Vasc Dis Res. 2008;5(3):177-83; Diabetes Care. 2006;29(6):1220-6.

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Safety

Muscle-related AEs in DM patients

Similar rates of muscle-related AEs were observed and no cases of rhabdomyolysis were reported.

CARDS [1] Median duration of 3.9 years (n = 2838)	Atorvastatin 10 mg/day (n = 1428)	Placebo (n = 1410)
Treatment-related		
Leg cramps, %	0.8	0.7
Muscle atrophy, %	0.1	0
Myalgia, %	1.0	1.2
Myasthenia, %	0.2	0.1
Myopathy, %	0.1	0
Myositis, %	0	0.1

Subgroup analysis of TNT [2] Median duration of 4.9 years (n = 1501)	Atorvastatin 80 mg/day (n = 748)	Atorvastatin 10 mg/day (n = 753)
Treatment-related		
Myalgia, %	2.4	3.6

AEs: adverse events; DM: diabetes mellitus.

1. Diab Vasc Dis Res. 2008;5(3):177-83; 2. Diabetes Care. 2006;29(6):1220-6.

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Liver enzymes-related AEs in DM patients

Safety

Similar rates of liver enzymes-related AEs were observed.

CARDS [1]
Median duration of 3.9 years (n = 2838)

	Atorvastatin 10 mg/day (n = 1428)	**Placebo** (n = 1410)
Single elevations in ALT ≥ 3 x ULN, %	0.9	0.6
Persistent elevations in ALT ≥ 3 x ULN, %	0.2	0.1
Single elevations in AST ≥ 3 x ULN, %	0.4	0.3
Persistent elevations in AST ≥ 3 x ULN, %	0	0

Subgroup analysis of TNT [2]
Median duration of 4.9 years (n = 1501)

	Atorvastatin 80 mg/day (n = 748)	**Atorvastatin 10 mg/day** (n = 753)
Persistent elevations in ALT and/or AST > 3 x ULN, %	0.9	0.4

AEs: adverse events; DM: diabetes mellitus; ALT: alanine transaminase; ULN: upper limit of normal; AST: aspartate transaminase.

1. Diab Vasc Dis Res. 2008;5(3):177-83; 2. Diabetes Care. 2006;29(6):1220-6.

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Safety

LDL-C and AEs in DM patients

No association between LDL-C level and incidence of AEs was observed.

Baseline LDL-C*	< 2.75 mmol/L (< 106 mg/dL)		2.75 to < 3.40 mmol/L (106 mg/dL to < 131 mg/dL)		≥ 3.40 mmol/L (≥ 131 mg/dL)	
	Atorvastatin (n=475)	Placebo (n=471)	Atorvastatin (n=469)	Placebo (n=477)	Atorvastatin (n=484)	Placebo (n=461)
LDL-C at one year, mmol/L	1.37 (1.02, 1.67)	2.46 (1.99, 2.91)	1.82 (1.53, 2.15)	3.16 (2.77, 3.53)	2.22 (1.88, 2.57)	3.73 (3.38, 4.16)
LDL-C at one year, mg/dL *	53.0 (39.4, 64.6)	95.1 (77.0, 113)	70.4 (59.2, 83.1)	122 (107, 137)	85.8 (72.7, 99.4)	144 (131, 161)
AE parameter						
Cancer **	22 (4.6)	24 (5.1)	22 (4.7)	19 (4.0)	25 (5.2)	29 (6.3)
Hypaesthesia	14 (3.0)	19 (4.0)	18 (3.8)	13 (2.7)	10 (2.1)	15 (3.3)
Myalgia	20 (4.2)	21 (4.5)	19 (4.1)	23 (4.8)	18 (3.7)	23 (5.0)
Neuropathy†	41 (8.6)	41 (8.7)	43 (9.2)	32 (6.7)	43 (8.9)	45 (9.8)
Paraesthesia	17 (3.6)	25 (5.3)	20 (4.3)	23 (4.8)	18 (3.7)	24 (5.2)

* To convert the values for cholesterol from mmol/L to mg/dL, divide by 0.02586; ** All preferred terms which contain carcinoma, melanoma or leukaemia;
† All preferred terms which contain neuropathy, neuritis or neuralgia.
LDL-C: low-density lipoprotein cholesterol; AEs: adverse events; DM: diabetes mellitus; LDL cholesterol values are median (Q1, Q3); other values are number of patients (%).

Diab Vasc Dis Res. 2008;5(3):177-83.

Safety

Low LDL-C and AEs

FOURIER study: Very low LDL-C did not lead to significant differences in the rates of AEs

Adverse events, n (%)	Statin + PCSK9 inhibitor (n=13,769)	Statin + Placebo (n=13,756)
Any AEs	10,664 (77.4)	10,644 (77.4)
Serious AEs	3410 (24.8)	3404 (24.7)
Discontinuation*	226 (1.6)	201 (1.5)
Cataract	228 (1.7)	242 (1.8)
Neurocognitive event	217 (1.6)	202 (1.5)

* Thought to be related to the study agent.
LDL-C: low-density lipoprotein cholesterol; AEs; adverse events; PCSK9: proprotein convertase subtilisin-kexin type 9.

N Engl J Med. 2017;376(18):1713-22.

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Safety

New-onset diabetes

TNT study, n = 10001

Median duration of 4.9 years

With DM, n = 1501

Without DM, n = 8500

865 (10.2%) developed diabetes

425 from the atorvastatin 10 mg group

440 from the atorvastatin 80 mg group

DM: diabetes mellitus.

odds ratio = 1.04; *P* = 0.59

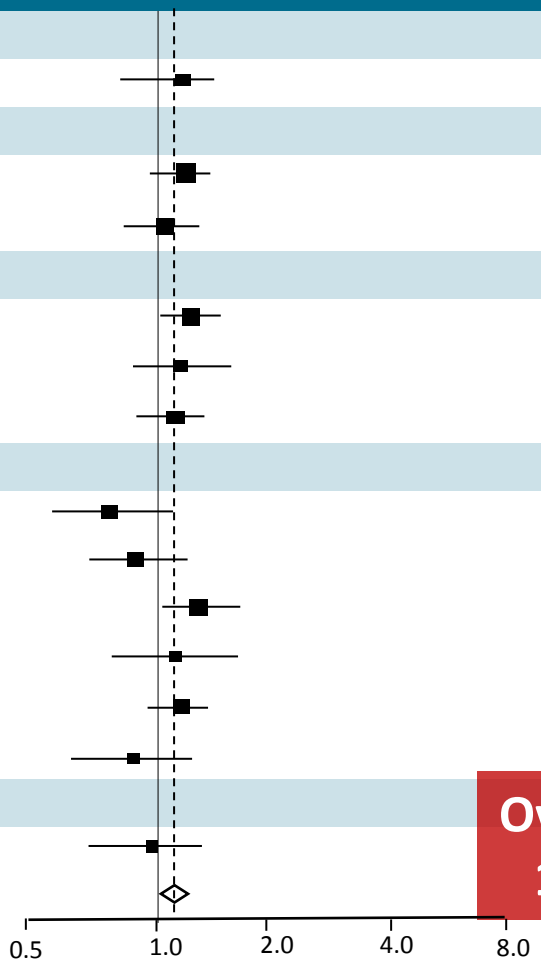
Diabetes Care. 2006;29(6):1220-6.

Safety

New-onset diabetes

A collaborative meta-analysis showed that statins slightly but significantly increased the risk of new-onset diabetes.

	n	Statin	Placebo or control	Odds ratio (95% Confidence interval)	Weight (%)
Atorvastatin					
ASCOT-LLA	7773	154	134	1.14 (0.89-1.46)	7.07%
Simvastatin					
HPS	14573	335	293	1.15 (0.98-1.35)	13.91%
4S	4242	198	193	1.03 (0.84-1.28)	8.88%
Rosuvastatin					
JUPITER	17802	270	216	1.26 (1.04-1.51)	11.32%
CORONA	3534	100	88	1.14 (0.84-1.55)	4.65%
GISSI HF	3378	225	215	1.10 (0.89-1.35)	9.50%
Pravastatin					
WOSCOPS	5974	75	93	0.79 (0.58-1.10)	4.24%
LIPID	6997	126	138	0.91 (0.71-1.17)	6.53%
PROSPER	5023	165	127	1.32 (1.03-1.69)	6.94%
MEGA	6086	172	164	1.07 (0.86-1.35)	8.03%
ALLHAT-LLT	6087	238	212	1.15 (0.95-1.41)	10.23%
GISSI PREVENZIONE	3460	96	105	0.89 (0.67-1.20)	4.94%
Lovastatin					
AFCAPS/TexCAPS	6211	72	74	0.98 (0.70-1.38)	3.76%
Overall (I^2 = 11.2%)				1.09 (1.02-1.17)	100%



Overall OR (95% CI)
1.09 (1.02–1.17)

Lancet. 2010;375(9716):735-42.

Safety

New-onset diabetes

FDA considered it as a class effect.[1]

However, clinical practice should not change because CV benefits of statins outweigh its disadvantages.[2]

FDA: Food and Drug Administration; CV: cardiovascular.

1. South Med J. 2016;109(3):167-73; 2. Lancet. 2010;375(9716):735-42.

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Take Home Messages

1

Diabetic dyslipidemia might be the main reason of atherosclerosis in diabetic patients.[1]

2

CARDS, ASCOT-LLA, TNT, and PROVE IT-TIMI demonstrated that **atorvastatin significantly improved CV outcomes**.[2-5]

3

A Taiwan study showed **LDL-C goal attainment rate increased significantly as the dose of atorvastatin increased**.[6]

4

Atorvastatin is **well** tolerated in Asian or diabetic population.[7-9]

1. J Clin Endocrinol Metab. 2001;86(3):965-71; 2. Lancet. 2004;364(9435):685-96; 3. Diabetes Care. 2005;28(5):1151-7; 4. Diabetes Care. 2006;29(6):1220-6; 5. Eur Heart J. 2006;27(19):2323-9; 6. Tzu Chi Medical Journal. 2013;25(3):168-74; 7. Cardiovasc Ther. 2016;34(6):431-40; 8. Diab Vasc Dis Res. 2008;5(3):177-83; 9. Diabetes Care. 2006;29(6):1220-6.