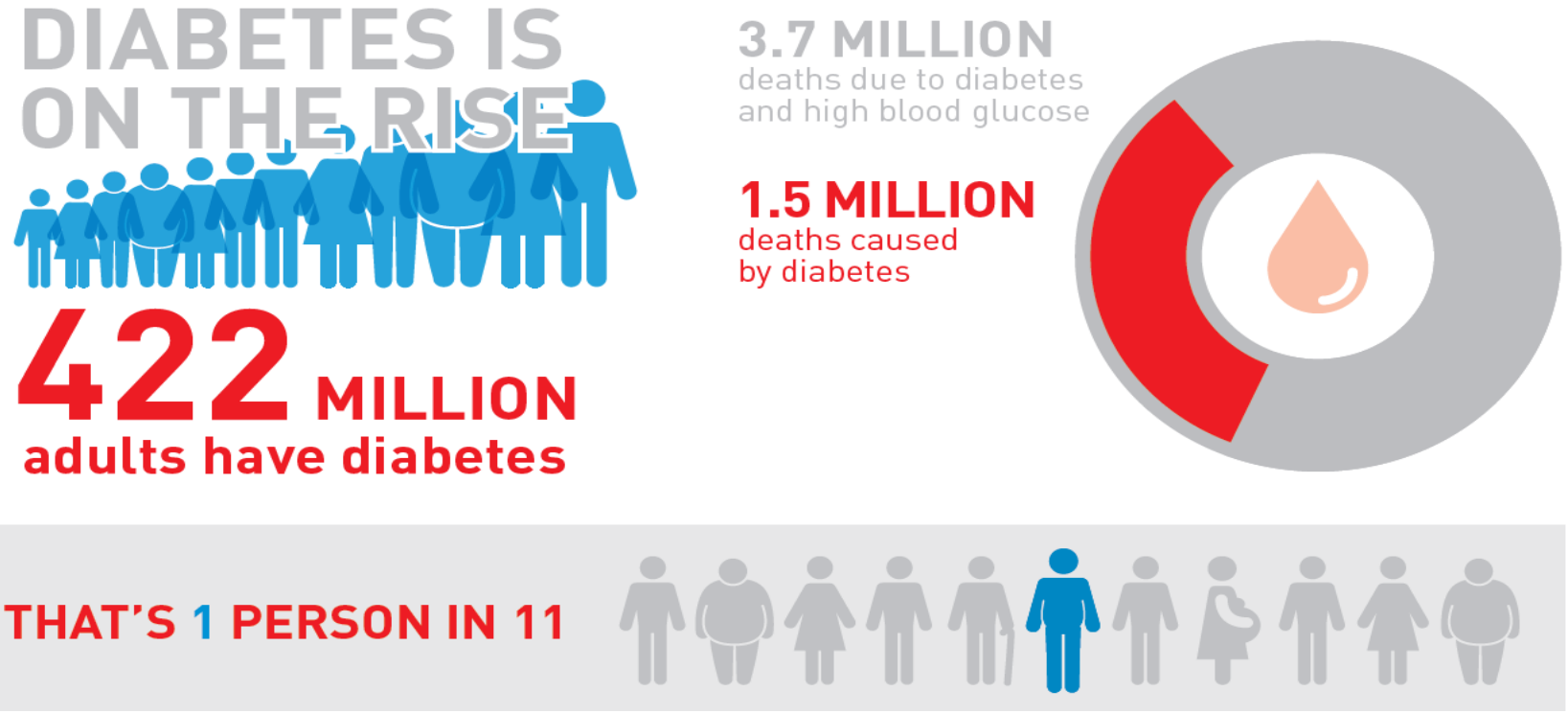
Statins in Diabetes

Introduction

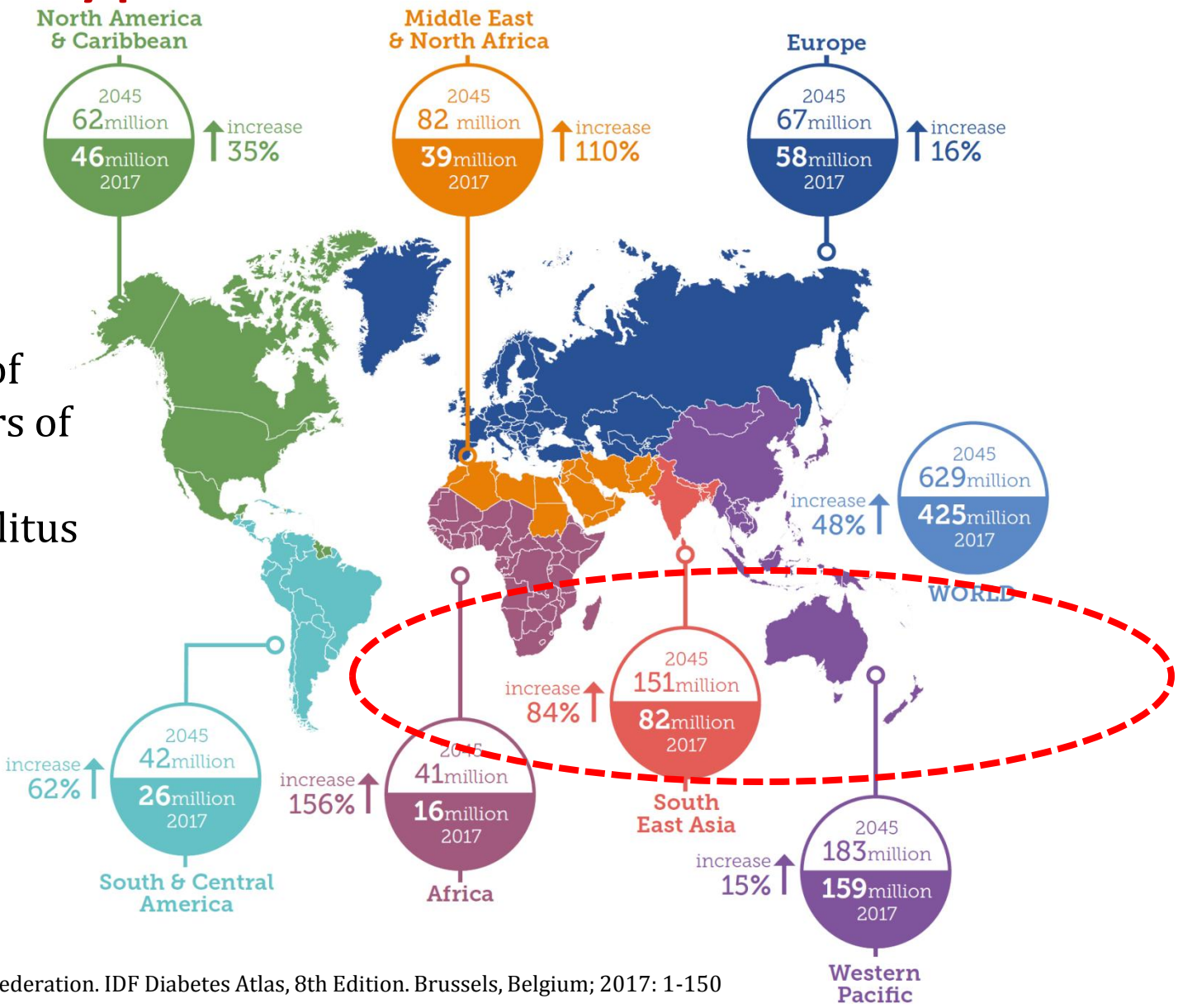
- The burden of Type 2 diabetes (T2D) is increasing exponentially in the world with an alarming rise in developing countries.



Available at http://www.who.int/mediacentre/factsheets/fs312/en/ accessed on 01-07-2019

Type II Diabetes Mellitus

- India is one of the epicenters of the global diabetes mellitus pandemic.



International Diabetes Federation. IDF Diabetes Atlas, 8th Edition. Brussels, Belgium; 2017: 1-150

Dyslipidemia Prevalence in India

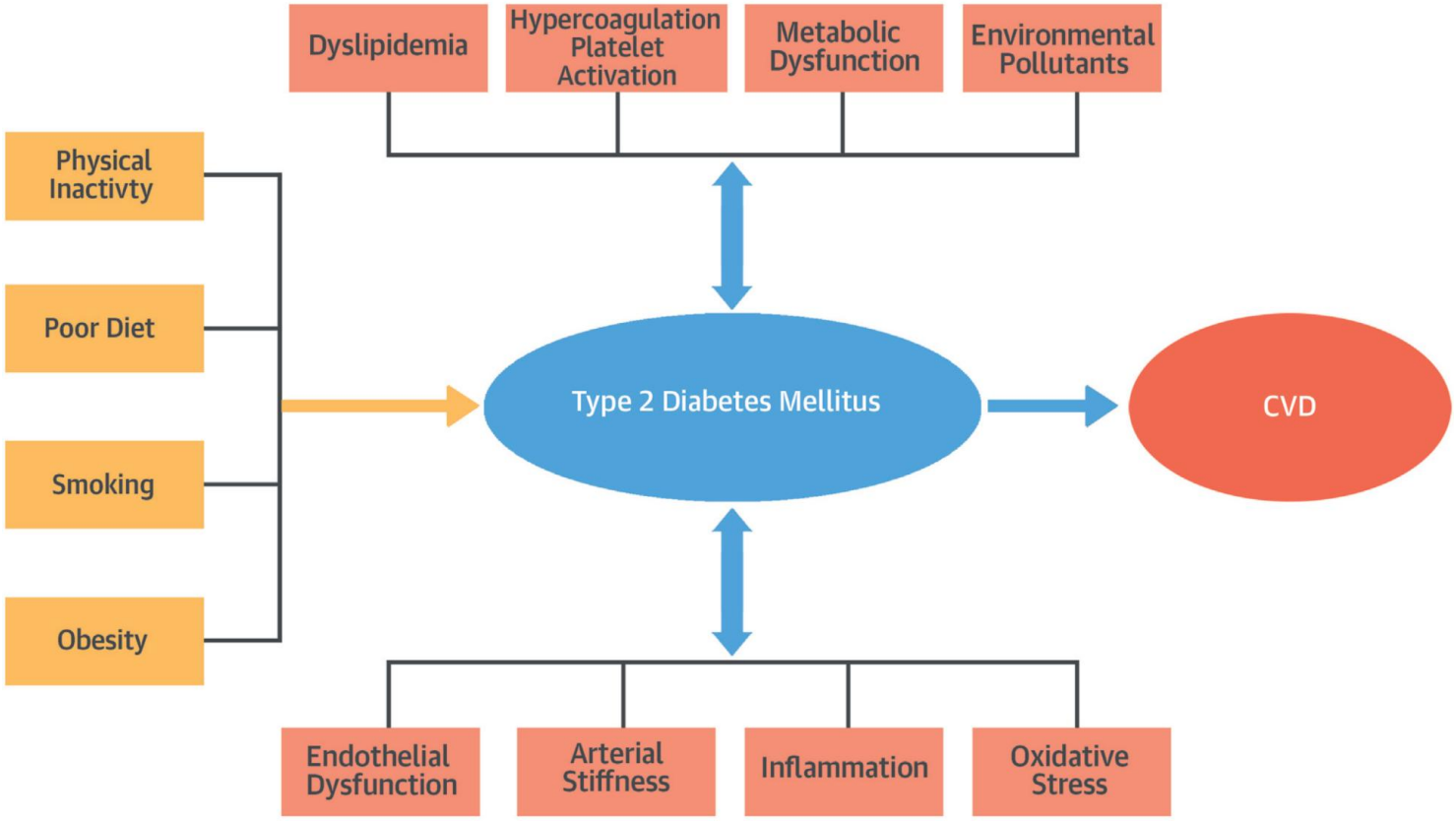
Study	Year reported	Sample size	Prevalence (%)	
			Men	Women
Indian Industrial Population Surveillance Study	2006	10,442	25.1	--
India Migration Study: Rural	2010	1,983	21.1	27.8
ICMR IDSP: Urban	2010	15,223	31.7	32.8
ICMR IDSP: Rural	2010	13,517	19.5	26.4
ICMR IDSP: Periurban/Urban Slum	2010	15,751	18.1	23.4
Indian Women's Health Study: Urban	2013	2,008	-	27.7
Indian Women's Health Study: Rural	2013	2,616	-	13.5
India Heart Watch	2014	6,123	25.1	24.9
ICMR INDIAB Study	2014	2,042	13.9	

IDSP: Integrated Disease Surveillance Project

Enas EA et al. The Lipid Association of India Expert Consensus Statement 2016: J Clin Prev Cardiol 2016;5:62-6

Cardiovascular disease and Diabetes

- Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in diabetes
- Managing risk factors for CVD in patients with diabetes reduces both.



Newman, J.D. et al. J Am Coll Cardiol. 2017;70(7):883–93.

How to estimate total cardiovascular risk?

- The SCORE (Systematic Coronary Risk Estimation) charts are used.
- SCORE, which estimates the 10 year risk of fatal CVD, is recommended for risk assessment
- Can assist in making logical management decisions and may help to avoid both under- and over treatment.

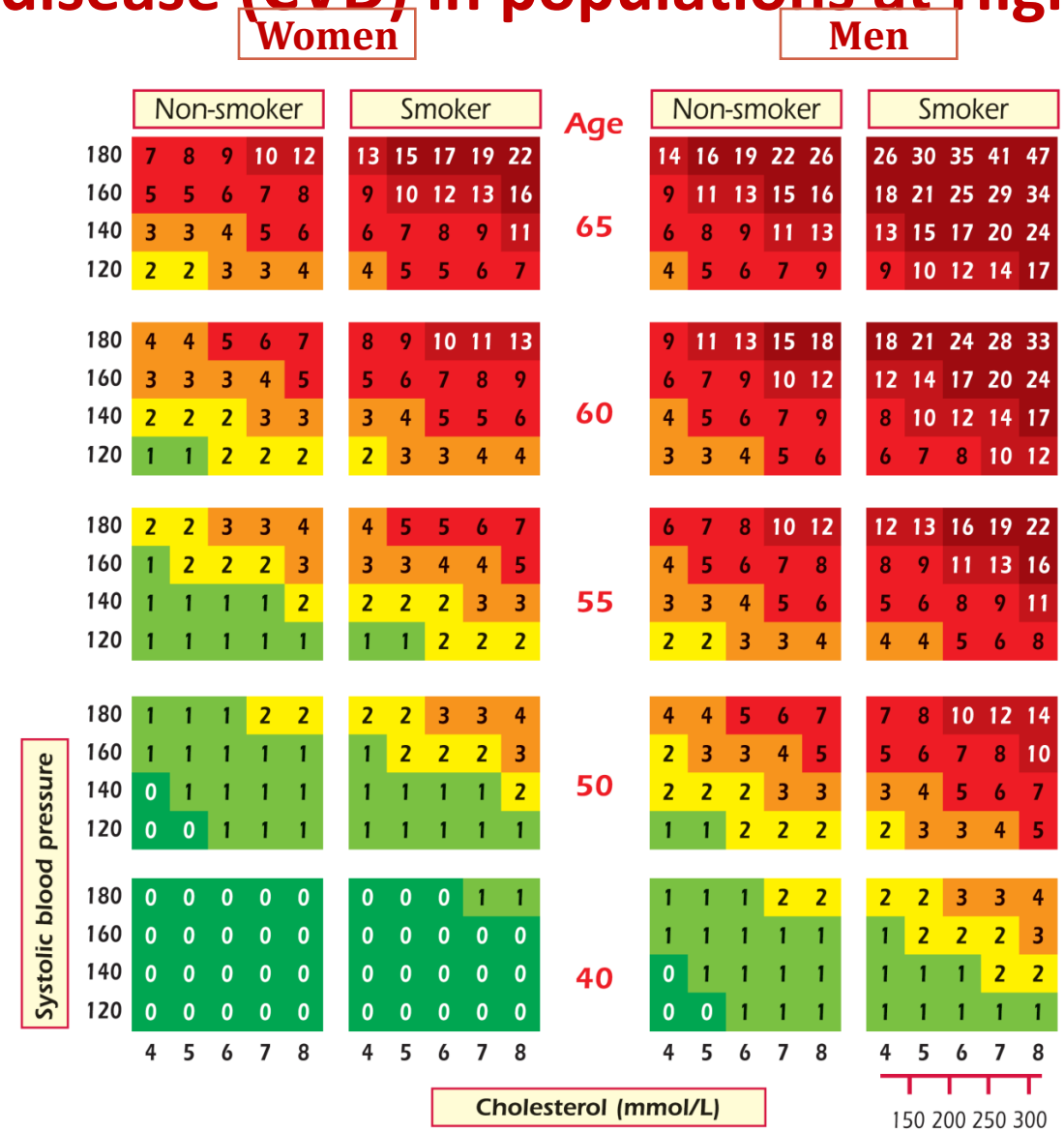
Recommendation for how to estimate cardiovascular risk

Recommendation	Class[a]	Level[b]	Ref[c]
Total CV risk estimation, using a risk estimation system such as SCORE, is recommended for adults >40 years of age, unless they are automatically categorised as being at *high-risk* or *very high-risk* based on documented CVD, DM (>40 years of age), kidney disease or highly elevated single risk factor (Table 5).	I	C	11, 25

CV = cardiovascular; DM = diabetes mellitus; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at High CVD risk

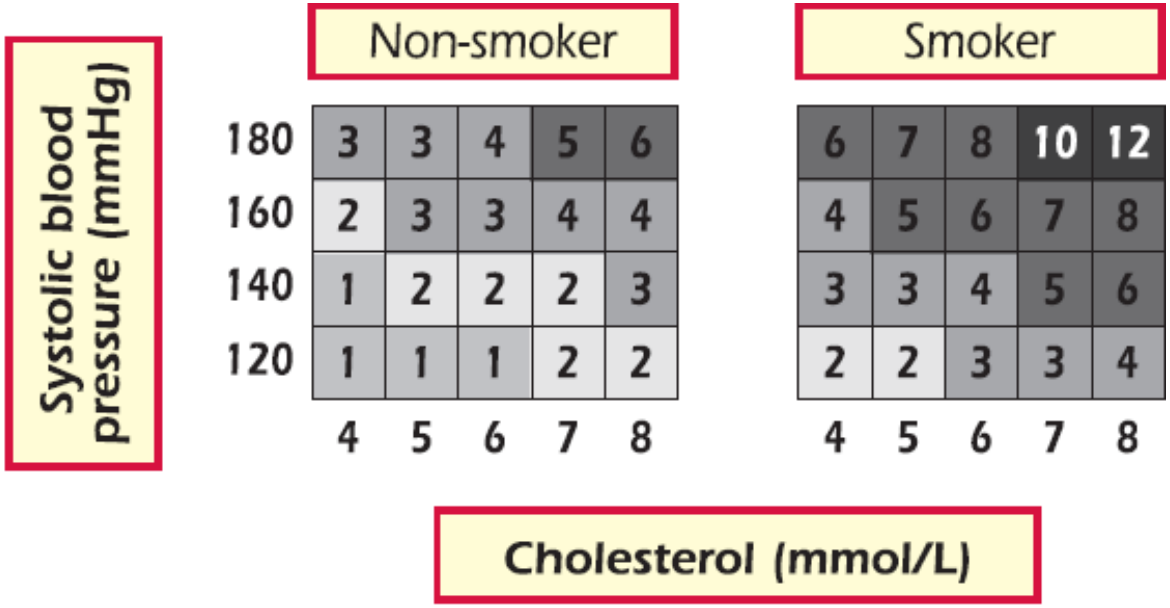


2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

Relative risk chart

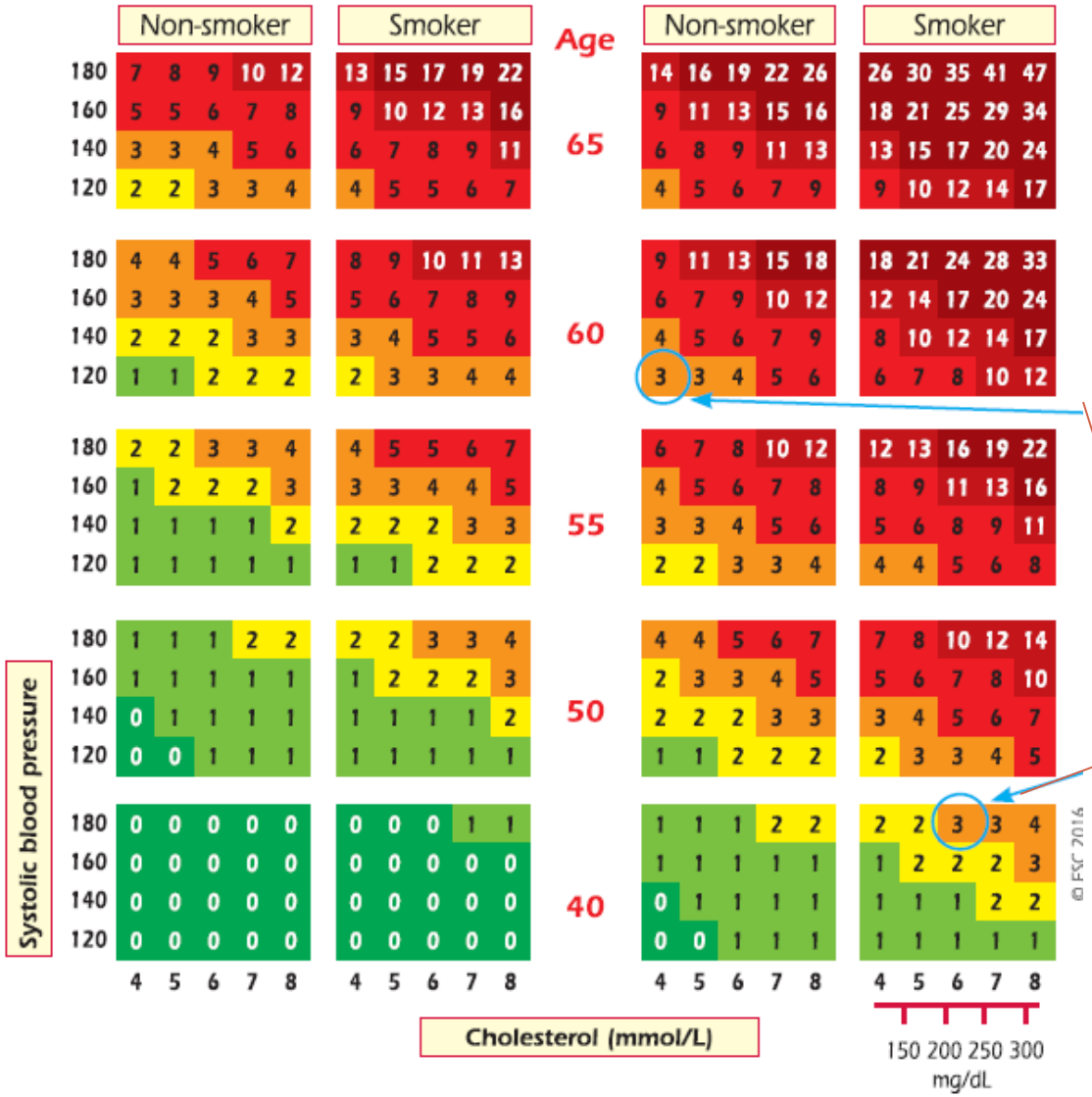
Chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary.

Help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication



Please note that this chart shows RELATIVE not absolute risk. Risks are RELATIVE to 1 in the bottom left. Thus a person in the top right hand box has a risk that is 12 times higher than a person in the bottom left.

Illustration of the risk age concept.



SCORE

- 15% and over
- 10%-14%
- 5%-9%
- 3%-4%
- 2%
- 1%
- < 1%

10-year risk of fatal CVD in populations at **High CVD risk**

The risk of this 40 yr old male smoker with risk factors is same (3%) as that of a 60- yr old man with ideal risk factor levels

There fore, HIS RISK AGE IS 60 years

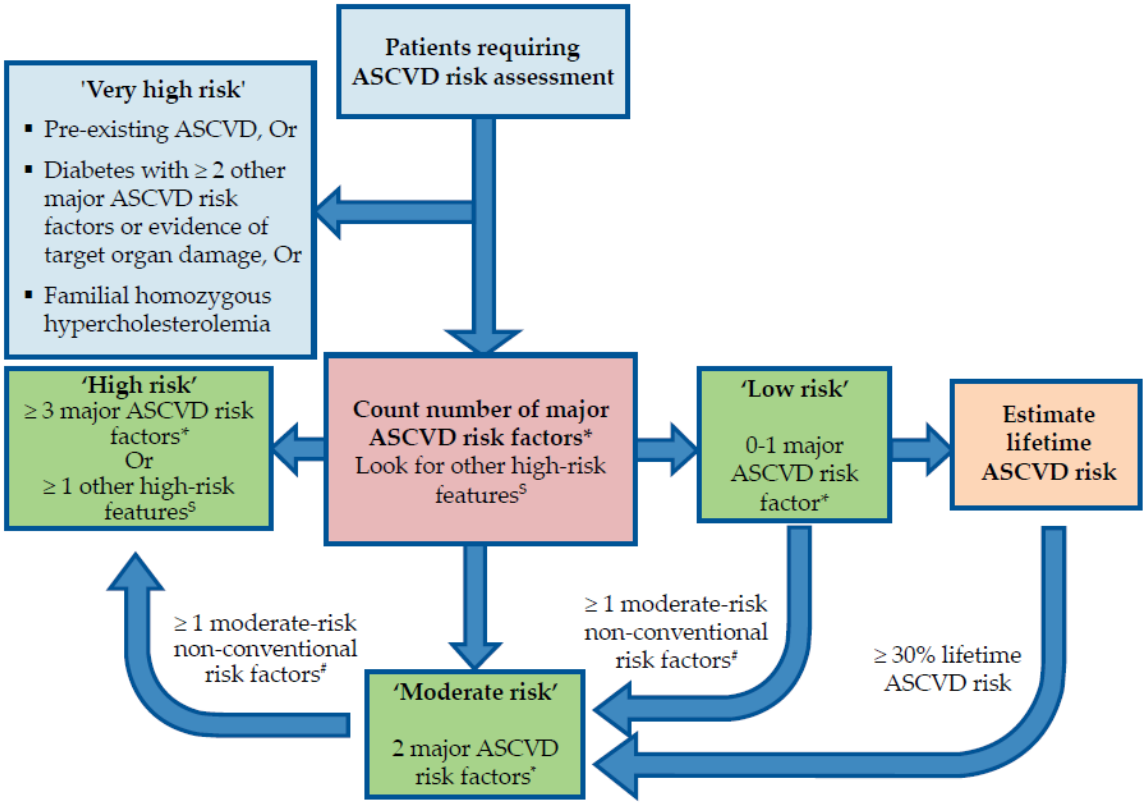
2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

ASCVD risk categories

Risk category	Conventional risk markers	Non-conventional risk markers (optional)
Very high risk	• Pre-existing ASCVD • Diabetes with- - evidence of end organ damage - ≥2 other major ASCVD risk factors • Familial homozygous hypercholesterolemia	• None
High risk: (>15% risk of ASCVD death, MI or stroke over a period of 10 years)	• ≥3 major ASCVD risk factors.* • Diabetes with 0-1 other major ASCVD risk factors and no evidence of end organ damage • CKD stage 3B or 4 • Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia) • Extreme of a single risk factor - e.g. LDL-C >190 mg/dL, strong family history of premature ASCVD, heavy smoker	• CAC score ≥300 Agatston units • Non-stenotic carotid plaque • Lp(a) ≥50 mg/dL
Moderate risk: (5-15% risk of ASCVD death, MI or stroke over a period of 10 years)	• 2 major ASCVD risk factors.*	• CAC score 100-299 Agatston units • Increased carotid intima media thickness (CIMT) or aortic pulse wave velocity (PWV) • Lp(a) 20-49 mg/dL • Metabolic syndrome
Low risk*: (<5% risk of ASCVD death, MI or stroke over a period of 10 years)	0-1 major ASCVD risk factors	None

*Estimation of lifetime ASCVD risk should be performed in these individuals and if the estimated risk is ≥30%, the person should be categorized as being at 'moderate risk'.

Iyengar SS et al. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1 - Executive summaryJ Clin Prev Cardiol 2016;5:51-61



***Major ASCVD risk factors**

1. Age ≥ 45 years in males and ≥ 55 years in females
2. Family history of premature ASCVD
3. Current cigarette smoking or tobacco use
4. High blood pressure
5. Low HDL-C

$Other high-risk features

1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage
2. CKD stage 3B or 4
3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)
4. Extreme of single risk factor
5. Coronary calcium score ≥ 300
6. Non-stenotic carotid plaque
7. Lipoprotein (a) ≥ 50 mg/dL

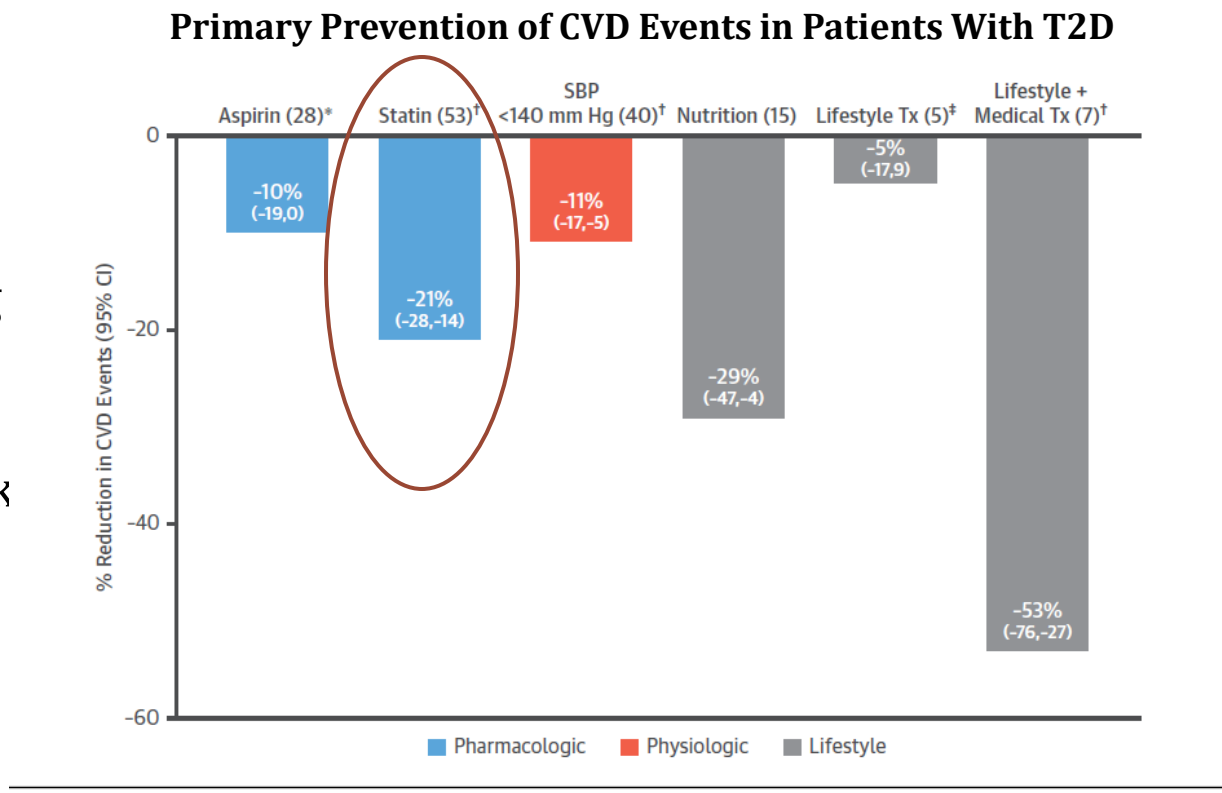
#Moderate-risk non-conventional risk factors

1. Coronary calcium score 100-299
2. Increased carotid IMT or aortic pulse wave velocity
3. Lipoprotein (a) 20-49 mg/dL
4. Metabolic syndrome

Iyengar SS et al. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1 - Executive summaryJ Clin Prev Cardiol 2016;5:51-61

The multifaceted approach

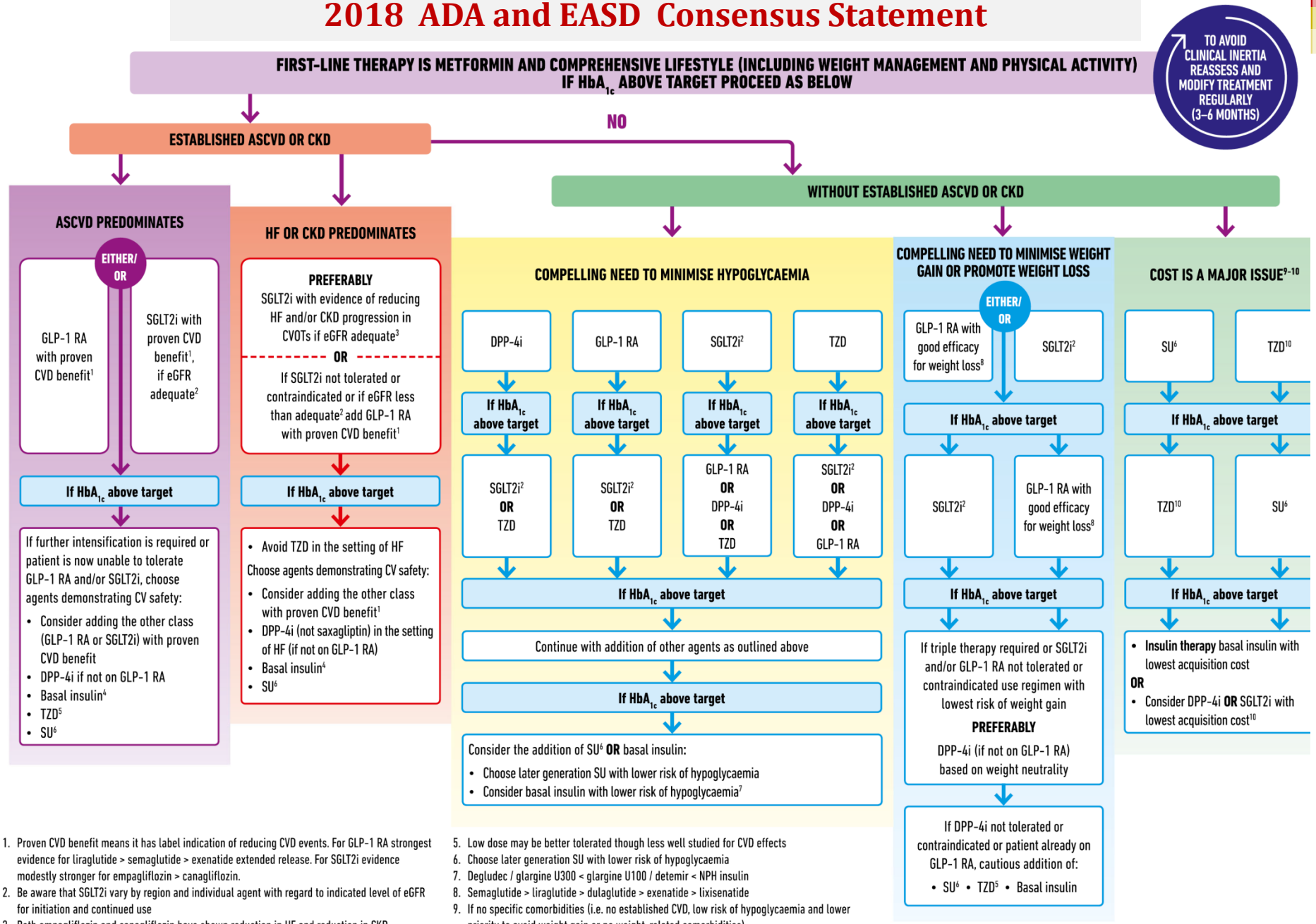
- Studies suggest that multifactorial interventions targeting several important risk factors simultaneously result in greater CV risk factor control.



CVD events are defined as cardiovascular death, myocardial infarction, or stroke and: *all-cause mortality; †revascularization or amputation; ‡hospitalization for angina. CI = confidence interval; CVD = cardiovascular disease; SBP = systolic blood pressure; T2D = type 2 diabetes; TX = treatment.

Newman, J.D. et al. J Am Coll Cardiol. 2017;70(7):883–93.

2018 ADA and EASD Consensus Statement

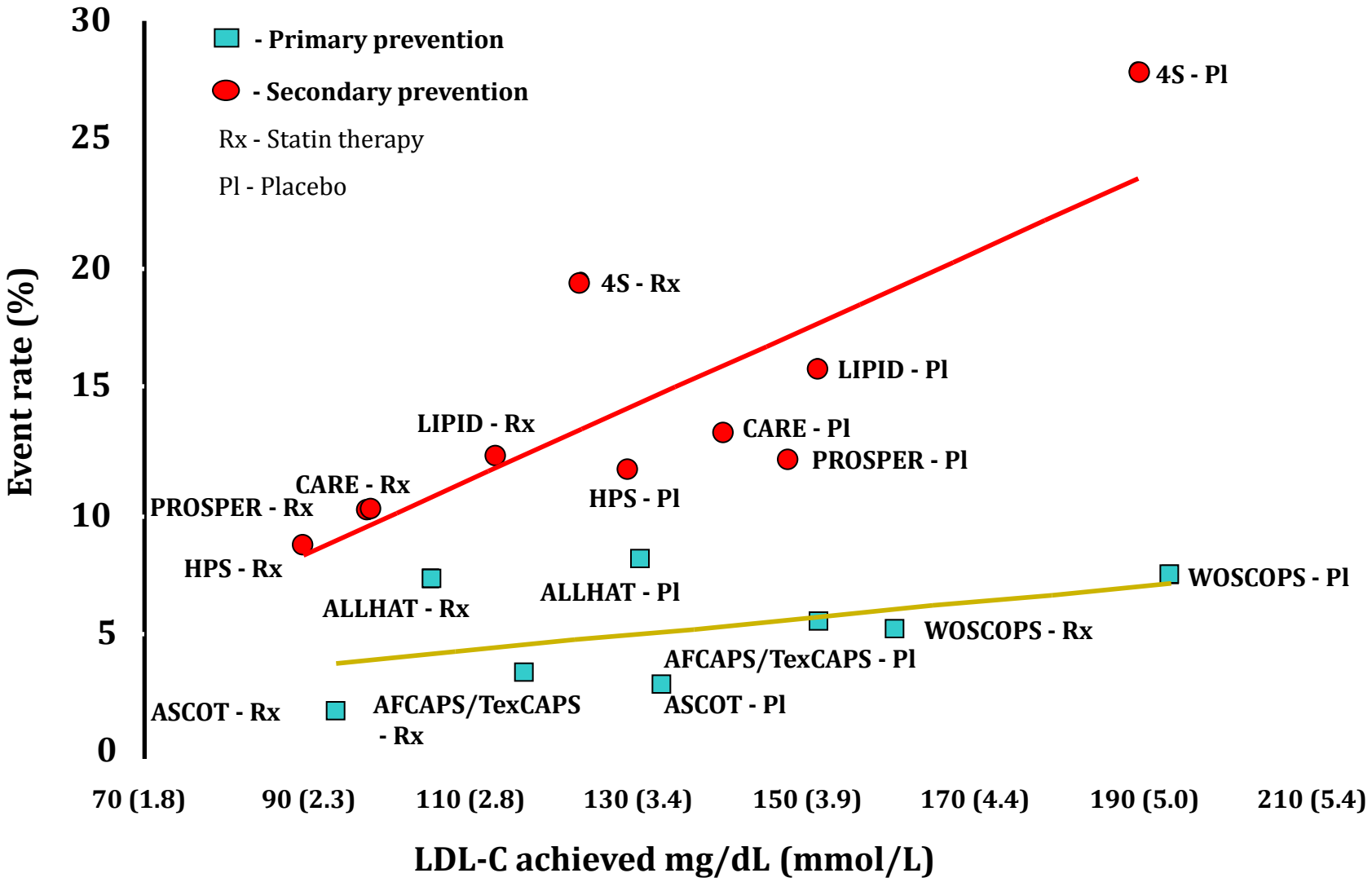


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine and [illegible]
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more [illegible]

2018 American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia 2018,61:2461–2498

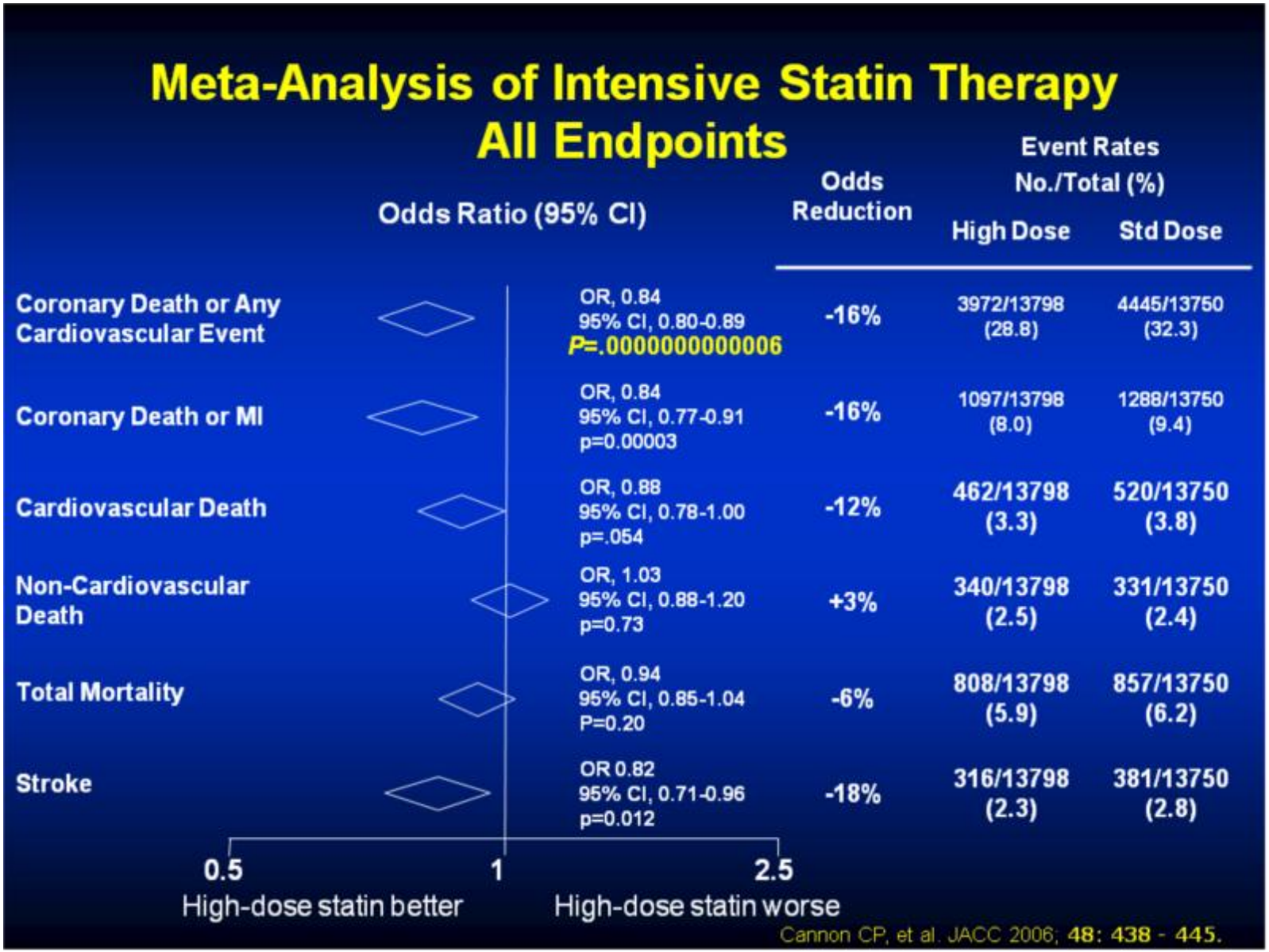
Dyslipidemia Management in Patients with Diabetes

Relationship between LDL-C and CV Event Rate



Jones PH et al. *Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial) Am J Cardiol* 2003;92:152–160

Meta-Analysis of Intensive Statin Therapy
All Endpoints



Cannon CP, et al. JACC 2006; **48: 438 - 445.**

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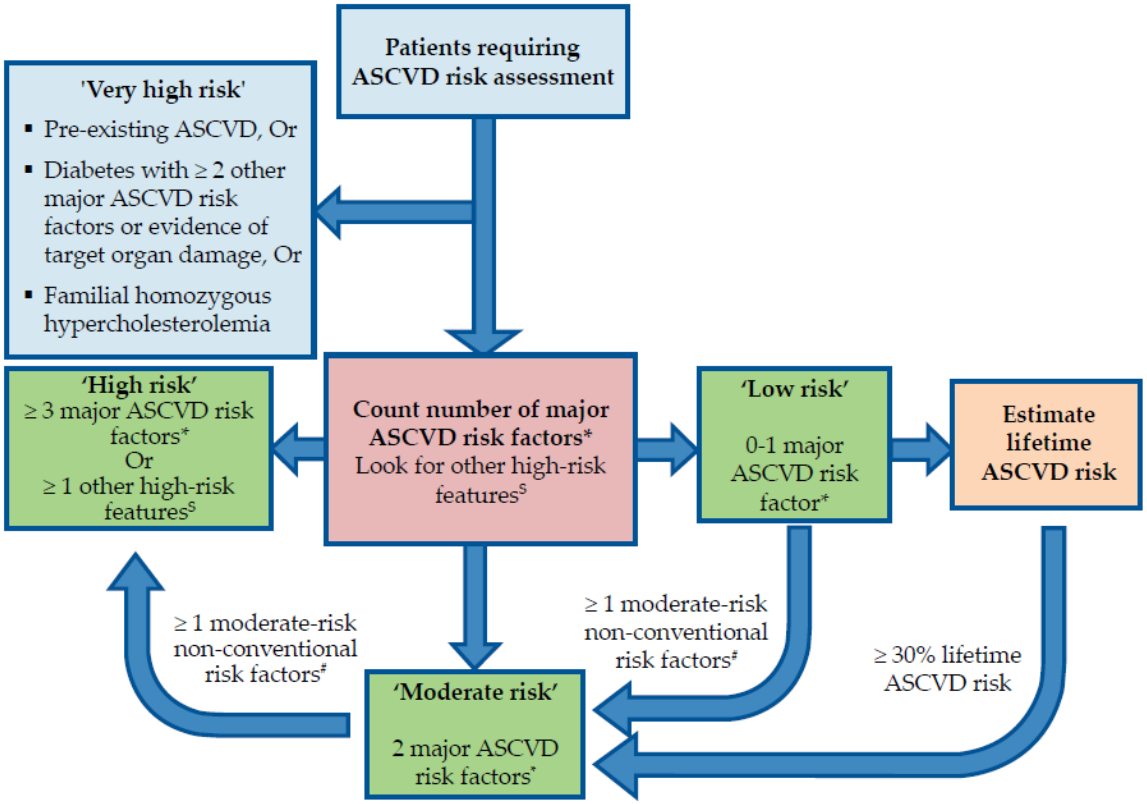

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Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	< 70 mg/dL	70 to < 100 mg/dL	100 to < 155 mg/dL	155 to < 190 mg/dL	> 190 mg/dL
< 1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥ 1 to < 5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
> 5 to < 10, or high risk	No lipid intervention	Lifestyle intervention consider drug*	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class/Level	IIa/A				
≥ 10 or very high risk	Lifestyle intervention consider drug*	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class/Level	IIa/A	IIa/A	I/A	I/A	I/A

2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

ESC Recommendations for treatment of dyslipidaemia in diabetes

Recommendations	Class	Level
In all patients with type I diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration.	I	C
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (<70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (<100 mg/dL) and for apoB is <80 mg/dL.	I	B
In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.	I	B

2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

Dietary recommendations to lower LDL-C and improve overall lipoprotein profile

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

2016 ESC/EAS Guidelines Catapano AL et al. Atherosclerosis. 2016 Sep 1. pii: S0021-9150(16)31267-9

Treatment goals and statin initiation thresholds according to ASCVD risk categories

Risk category	Treatment goal		Consider drug therapy	
	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-C (mg/dL)	Non-HDL- C (mg/dL)
Very high risk	< 50	< 80	≥ 50 (preferably in all)	≥ 80 (preferably in all)
Highrisk	< 70	< 100	≥ 70 (preferably in all)	≥ 100 (preferably in all)
Moderate risk	<100	<130	≥ 100	≥ 130
Low risk	<100	<130	≥ 130*	≥ 160*

*After an initial adequate non-pharmacological intervention for at least 3 months

Iyengar SS et al. Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1 - Executive summaryJ Clin Prev Cardiol 2016;5:51-61

ADA 2019 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)

*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 onrisk-benefitprofile andpresence ofASCVDrisk factors. ASCVD risk factors include LDL cholesterol $100 mg/dL (2.6 mmol/L), 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.

Standards Of Medical Care In Diabetes—2019 Diabetes Care. 2019 Jan;42(Suppl 1):S1-S205.

High-intensity and moderate-intensity statin therapy

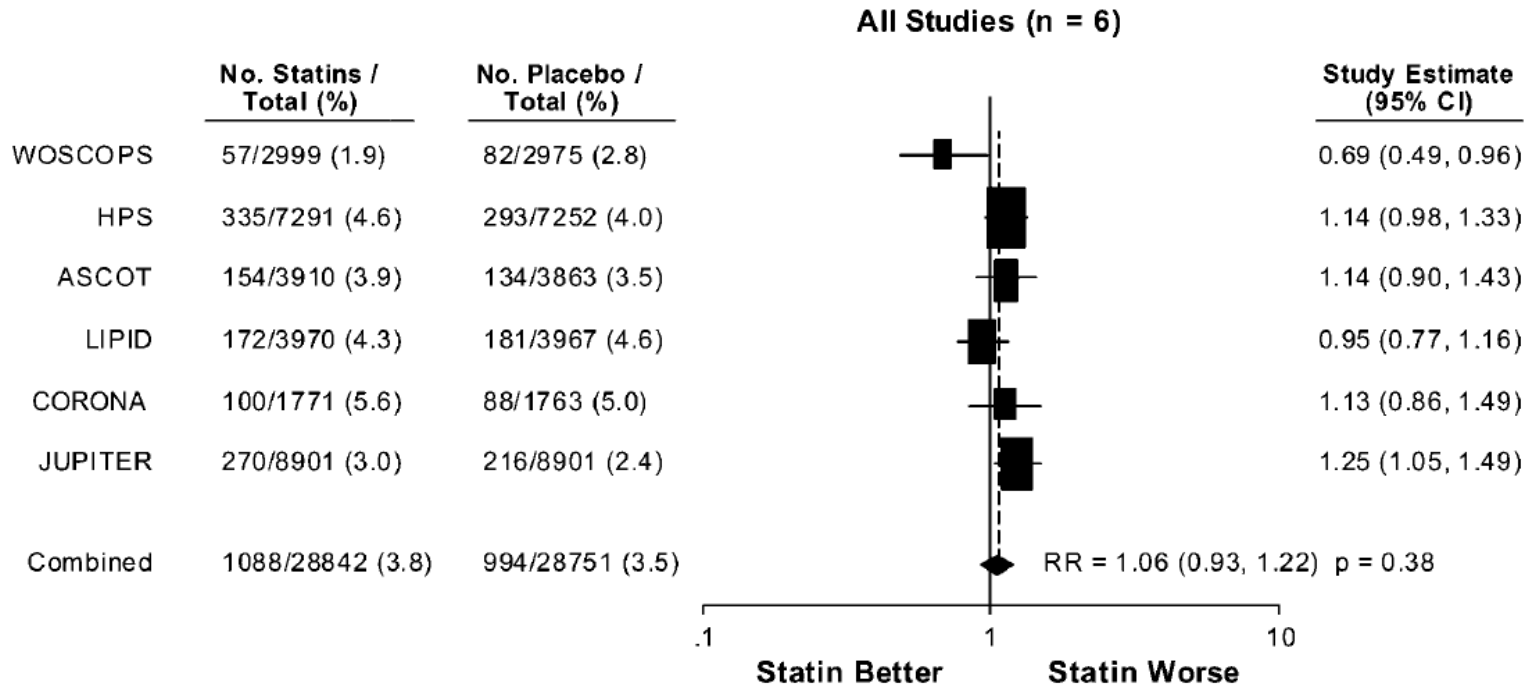
High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg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

Standards Of Medical Care In Diabetes—2019 Diabetes Care. 2019 Jan;42(Suppl 1):S1-S205.

Trial, year	Imaging modality	No. of patients	Duration	LDL-C achieved (mg/dL)	LDL-C/ HDL-C ratio	Primary endpoints
REVERSAL,[141] 2004	IVUS	502	1.6 years	Atorvastatin 79; Pravastatin 110	Atorvastatin 1.9; Pravastatin 2.5	Intensive lipid lowering reduced progression of coronary atherosclerosis as compared to less intensive therapy.
ASTEROID,[139] 2006	IVUS	507	2 years	Rosuvastatin 60.8; Placebo 130	Rosuvastatin 1.3; Placebo 3.2	There was significant reduction in all three pre-specified IVUS measures of disease burden (change in percent atheroma volume, change in atheroma volume in the 10-mm sub-segment with greatest disease severity at base line and change in normalized total atheroma volume for the entire coronary artery).
METEOR,[142] 2007	Carotid ultrasound	984	2 years	Rosuvastatin 78; Placebo 152	Rosuvastatin 1.5; Placebo 3.1	After two years, treatment with rosuvastatin was associated with statistically significant reduction in the rate of progression of CIMT in overall carotid segments, while the placebo group experience progression.
ORION,[143] 2008	MRI	43	2 years	Rosuvastatin 5 mg 96; Rosuvastatin 40 mg 57.7	Not available	Subjects whose wall volume regressed (n=16) had an on-treatment mean LDL-C of 69 mg/dL (-56%), whereas subjects whose wall volume progressed (n=19) had an LDL-C of 84 mg/dL (-45%).
SATURN,[144] 2011	IVUS	1039	104 weeks	Rosuvastatin 62.6; Atorvastatin 70.2	Rosuvastatin 1.3; Atorvastatin 1.5	For the primary IVUS endpoint, the extent of regression was similar for both the regimens (P=0.17). However, for the secondary IVUS endpoint, a greater degree of regression was observed with rosuvastatin compared with atorvastatin (P=0.01).
YELLOW,[145] 2013	NIRS IVUS	87	6-8 weeks	Rosuvastatin 58.4; Simvastatin 81.9	Rosuvastatin 1.5; Simvastatin 2.3	Aggressive lipid lowering therapy resulted in significant reduction in the lipid component of coronary atherosclerotic plaques as detected by NIRS in a short time frame (6-8 weeks).
PRECISE-IVUS,[146] 2015	IVUS	202	9-12 mths	Atorvastatin with ezetimibe 63.2; Atorvastatin alone 73.3		The absolute change in percent atheroma volume of a select target segment of a coronary artery from baseline to follow-up (the primary efficacy outcome) was greater with the dual lipid lowering strategy than with atorvastatin alone.

Statins and Diabetes Risk

- Several studies have reported a modestly increased risk of incident diabetes with statin use which may be limited to those with diabetes risk factors.



Rajpathak SN et al. Diabetes Care 2009;32:1924– 1929

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

- 13 statin trials with 91 140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years.
- Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity (I(2)=11%) between trials.
- Treatment of 255 (95% CI 150-852) patients with statins for 4 years resulted in one extra case of diabetes.

Sattar N et al. Lancet. 2010 Feb 27;375(9716):735-42.

Conclusion

- Statins provide risk reduction in a wide range of patients with diabetes who either have established CVD or are at high risk of developing atherothrombosis.
- National and International guidelines recommendations: All patients with diabetes and established CVD should be prescribed a statin unless contraindicated.
- Lifestyle modification should be addressed emphatically to help reduce the incident diabetes risk from statins as well as overall CVD risks.
- The clear benefits of statins on CVD likely outweigh any potential detrimental effects on glucose metabolism and diabetes risk.

Diabetes Care. 2019 Jan;42(Suppl 1):S1-S205.
Davies JM et al. Diabetologia 2018,61:2461–2498
Rajpathak SN et al. Diabetes Care 2009;32:1924–1929
Subedi et al. Diabetes Spectrum 2013;26(3):156-164

THANKYOU