Optimal Tx for Patients with Dyslipidemia: A MUST Tx for High Risk Patients

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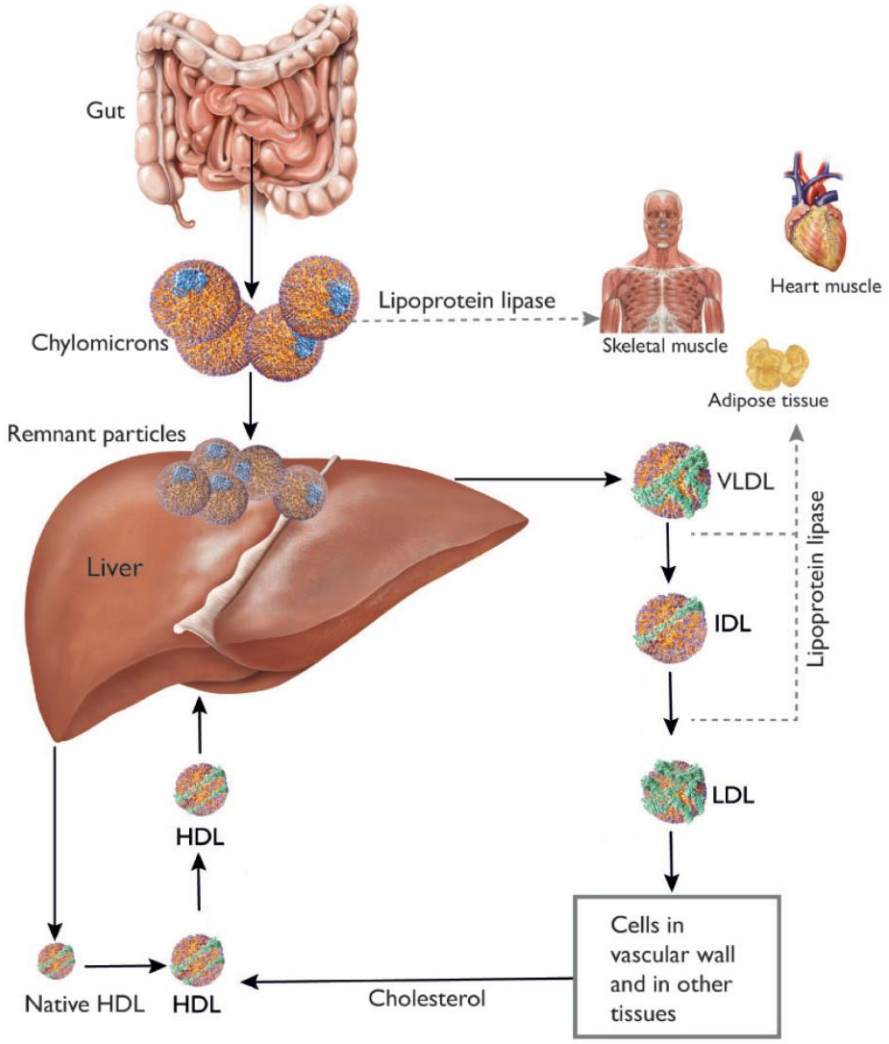
- 2019 ESC Lipid Guideline Key Massages
- High potency statin in high risk patients
- Conclusions

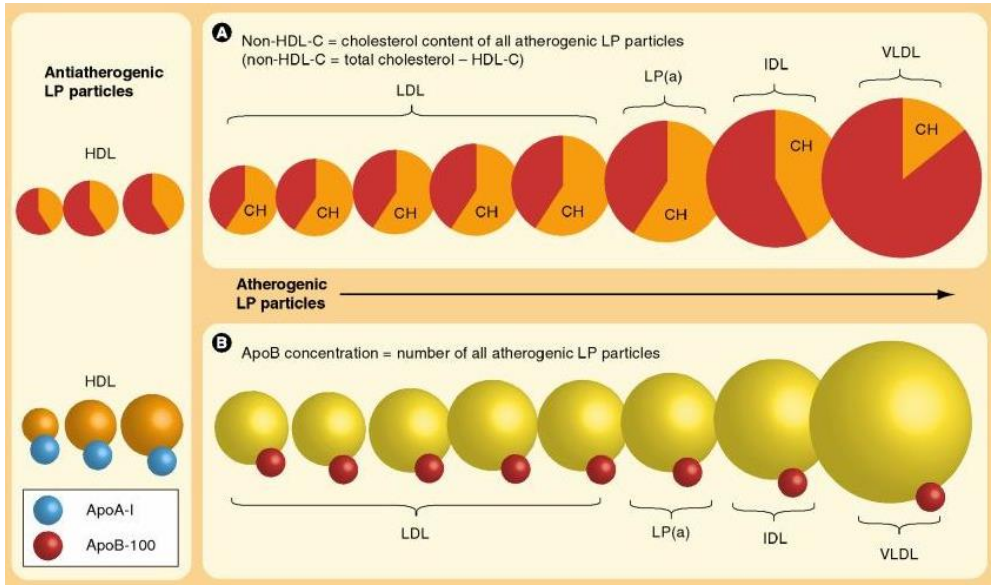
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

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

European Heart Journal (2019) 00, 178

Lipoproteins and Cholesterol Transport



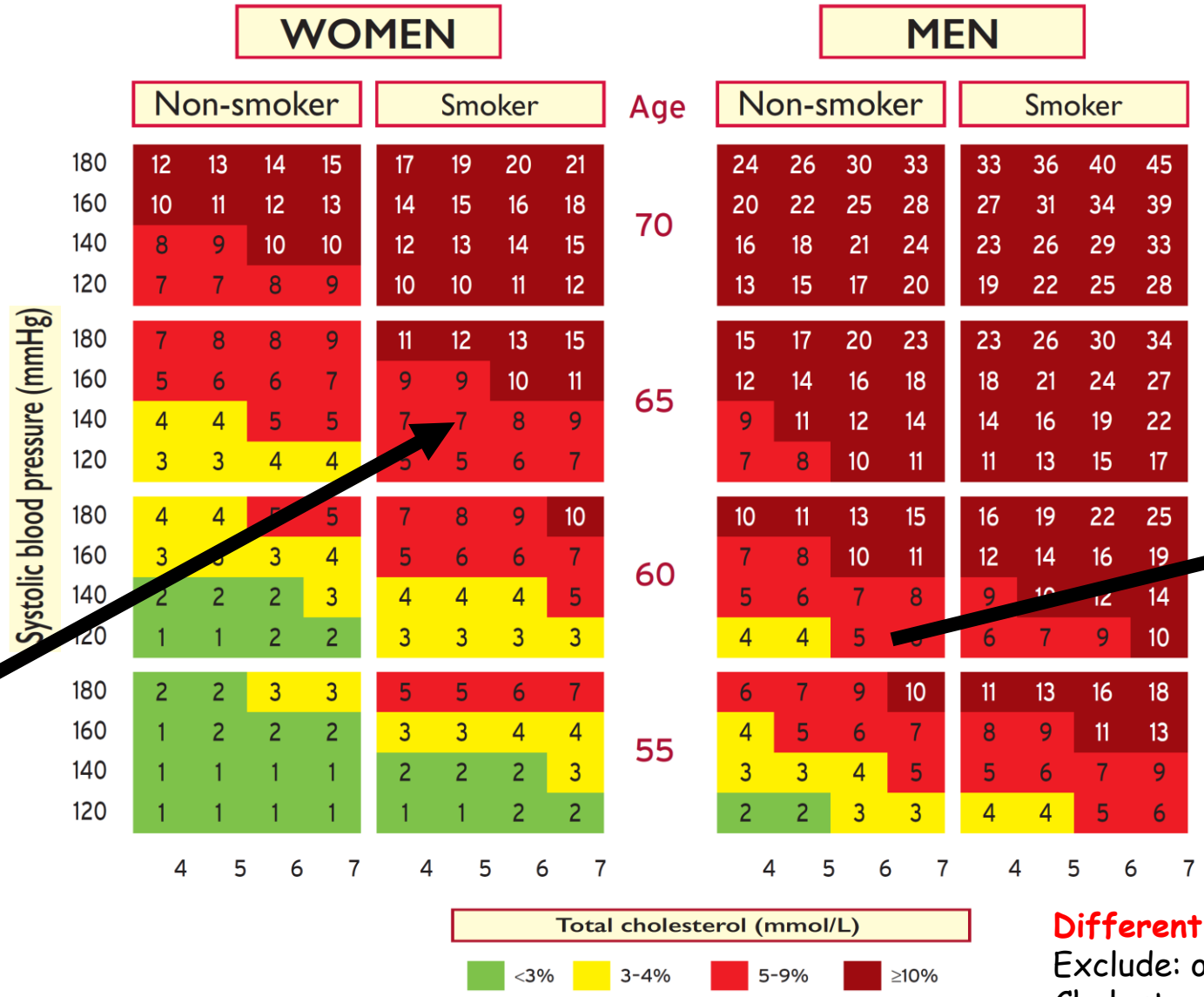


Lipid Hypothesis ⇒ LDL ↓, HDL↑ ⇒ atherosclerosis ↓

European Heart Journal (2019) 00, 178

SCORE Cardiovascular Risk Chart
10-year risk of fatal CVD

High-risk regions of Europe



Female, smoker, 65 y/o
T-chol 5 mmol/L, SBP
140mmHg, risk score 7

Male, non- smoker, 60 y/o
T-chol 6 mmol/L, SBP:120 mmHg
risk score 5

Different regions of Europe

Exclude: overt CVD, type 1,2 DM, CKD, FH,
Cholesterol: 1 mmol/L = 38.67 mg/dL

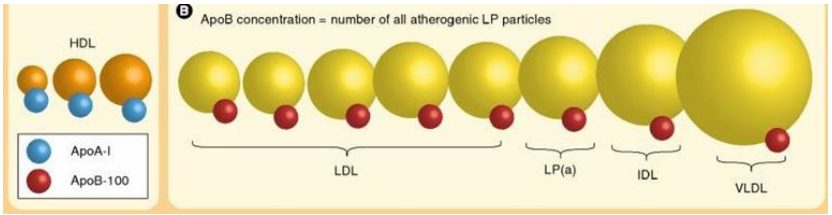
Cardiovascular Risk Categories

Very-high-risk	People with any of the following: Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE >10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (≥310 mg/dL), LDL-C ≥4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE >5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

European Heart Journal (2019) 00, 178

Lipid Analyses for CVD Risk Estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C



European Heart Journal (2019) 00, 178

Treatment Goals for LDL-C

Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120] **LDL-C: 50%↓ and <55mg/dL**	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36] **LDL-C: 50%↓ and <55mg/dL**	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered. **LDL-C: 50%↓ and <55mg/dL**	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120] **LDL-C: <40mg/dL**	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35] **LDL-C: 50%↓ and <70mg/dL**	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34] **LDL-C: <100mg/dL**	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36] **LDL-C: <116mg/dL**	IIb	A

European Heart Journal (2019) 00, 178

Treatment Targets and Goals for CVD Prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL). **Moderate risk:** A goal of <2.6 mmol/L (<100 mg/dL). **Low risk:** A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Pharmacological LDL-C Lowering

It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For secondary prevention in patients at very-high risk not achieving their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C

European Heart Journal (2019) 00, 178

Drug Tx for High TG

Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with HTG [TGs >2.3 mmol/L (>200 mg/dL)].	I	B
In high-risk patients with TG levels between 1.5 - 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with a statin.	IIa	B

European Heart Journal (2019) 00, 178

Management of Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives having tendon xanthomas, in people with severely elevated LDL-C levels [in adults >5 mmol/L (>190 mg/dL), in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients.	I	C
It is recommended that FH is diagnosed using clinical criteria and confirmed, when possible, with DNA analysis.	I	C
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk.	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve a >50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
Treatment with a PCSK9 inhibitor is recommended in very-high risk FH patients if the treatment goal is not achieved on a maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C

European Heart Journal (2019) 00, 178

Treatment of Dyslipidemias in Older People

Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged <75 years.	I	A
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

European Heart Journal (2019) 00, 178

Treatment of Dyslipidemias in DM

In patients with T2DM at very-high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended. **LDL-C: 50%↓ and <55mg/dL**	I	A
In patients with T2DM at high risk,[c] an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended. **LDL-C: 50%↓ and <70mg/dL**	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.[c]	I	A
Statin therapy is not recommended in pre-menopausal patients with or without DM who are considering pregnancy, or not using adequate contraception.	III	C

European Heart Journal (2019) 00, 178

Management of Patients with ACS

In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values.	I	A
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B

European Heart Journal (2019) 00, 178

Ischemic Stroke, CKD, PAD

Lipid-lowering therapy for prevention of ASCVD events in patients with prior ischaemic stroke		
Patients with a history of ischaemic stroke or TIA are at very-high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy.	I	A
Lipid management in patients with moderate-to-severe (Kidney Disease Outcomes Quality Initiative stages 3–5) CKD		
It is recommended that patients with stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	I	A
In patients with dialysis-dependent CKD who are free of ASCVD, commencement of statin therapy is not recommended.	III	A
Lipid-lowering drugs in patients with PAD (including carotid artery disease)		
In patients with PAD, lipid-lowering therapy—including a maximum tolerated dose of a statin, plus ezetimibe, or a combination with a PCSK9 inhibitor if needed—is recommended to reduce the risk of ASCVD events.	I	A

- 2019 ESC Lipid Guideline Key Massages
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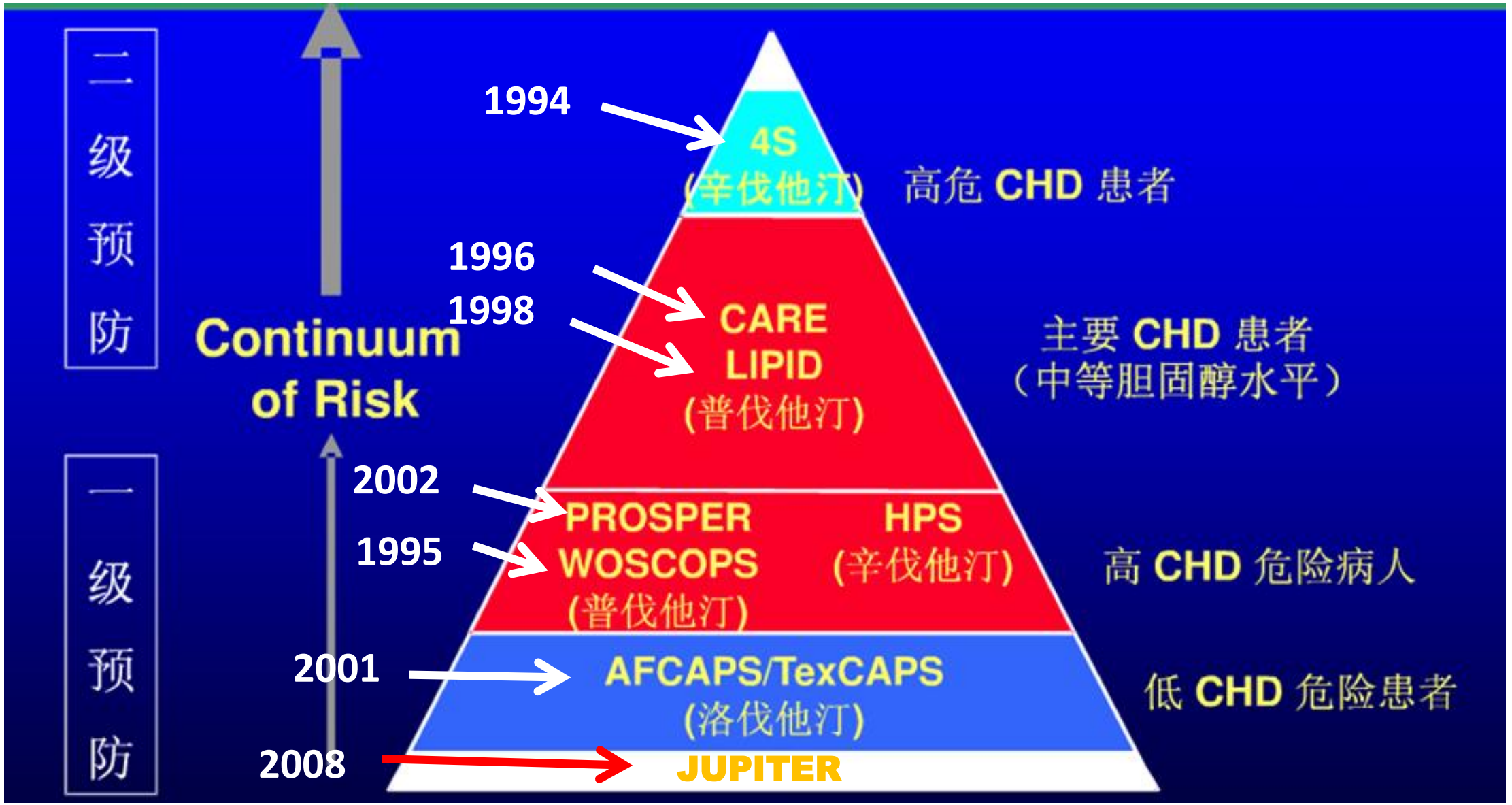
Potency of Statin

U.S Food and Drug Administration

Rosuvastatin	Atorva.	Fluva.	Pitava.	Lova.	Prava.	Ezitamibe /Simva.	Simva.	%↓ LDL-C
		40 mg	1 mg	20 mg	20 mg		10 mg	30%
	10 mg	80 mg	2 mg	40 mg or 80 mg	40 mg		20 mg	38%
5 mg	20 mg		4 mg	80 mg	80 mg	10/10 mg	40 mg	41%
10 mg	40 mg					10/20 mg	80 mg	47%
20 mg	80 mg					10/40 mg		55%
40 mg						10/80 mg		63%

http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#aihp

Milestone Study in Statin Tx

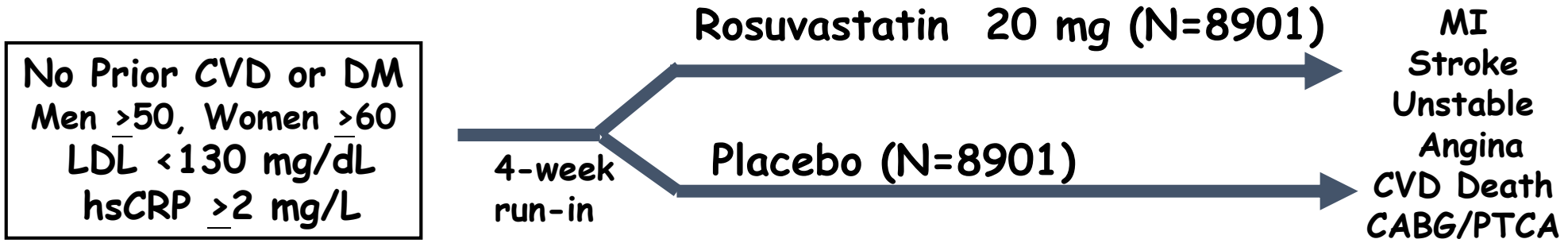


Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

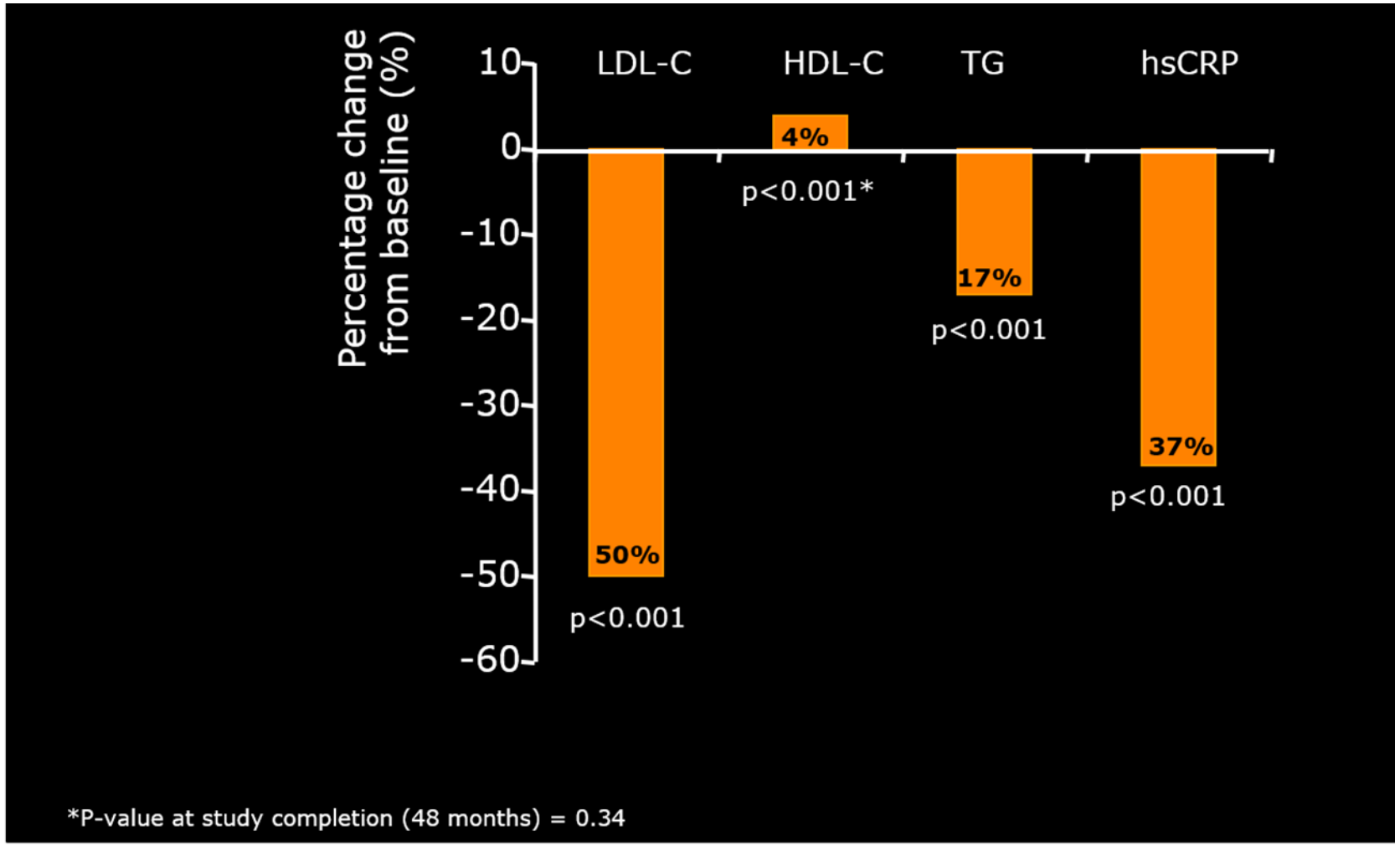
N Engl J Med 2008;359:2195-207

JUPITER Trial Design



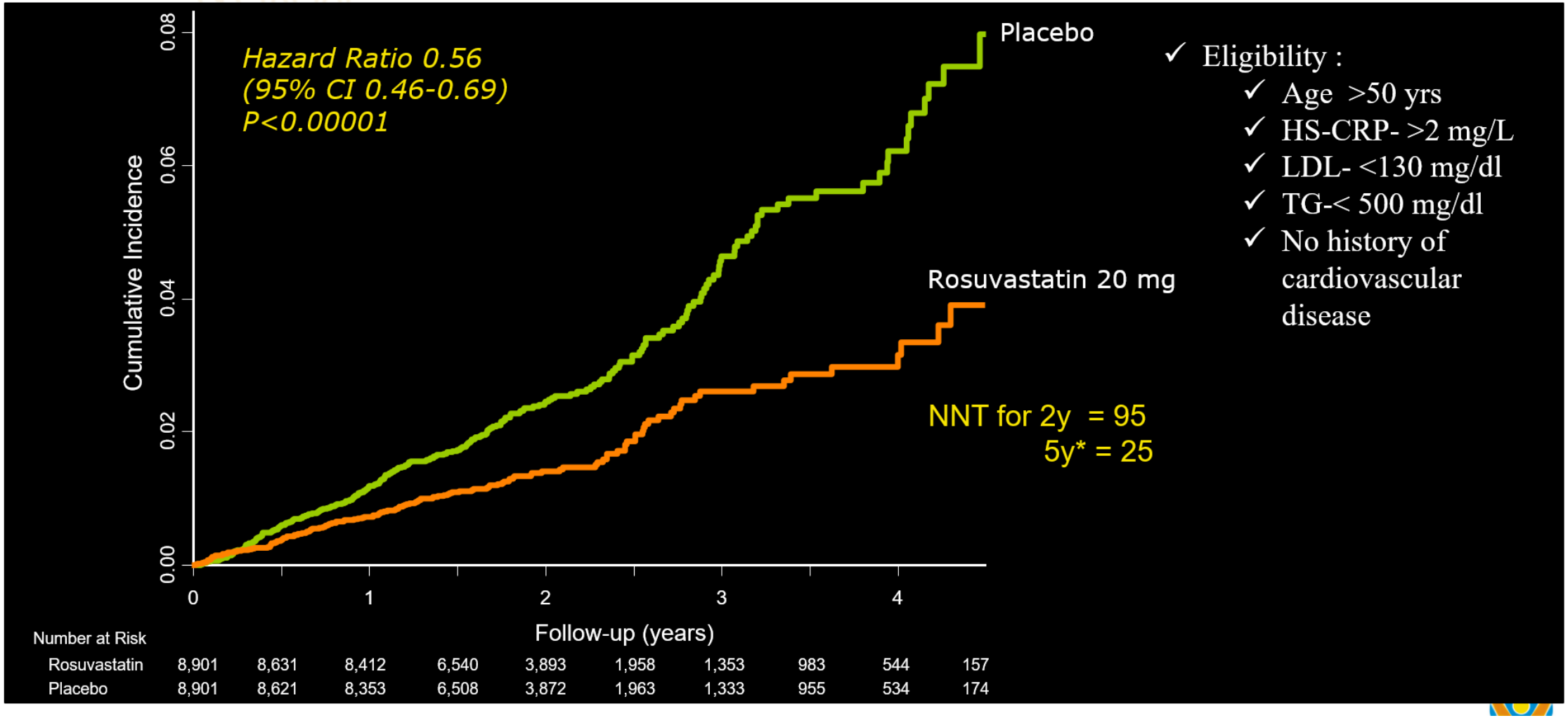
Ridker et al, Circulation 2003;108:2292-2297.

CRESTOR 20mg : Effects on LDL-C, HDL-C, TG and hsCRP at 12 months



Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

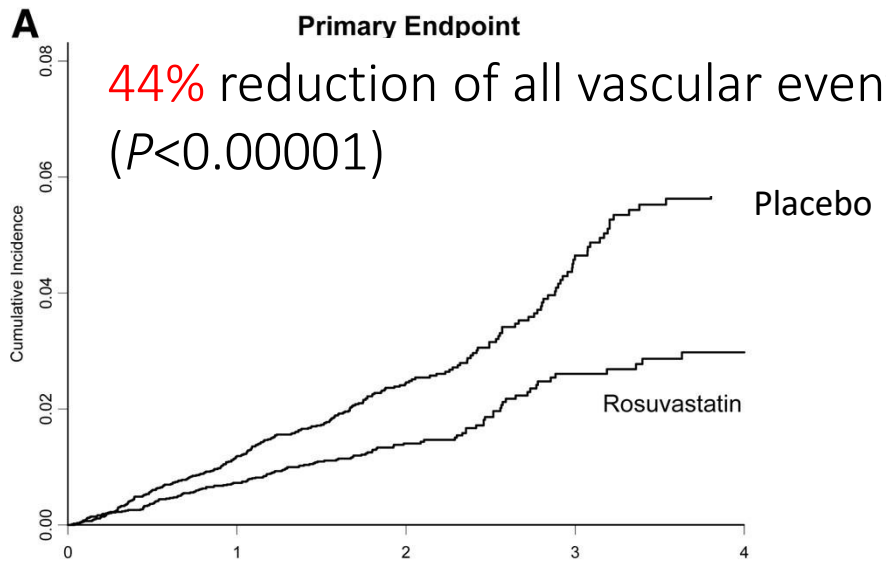
JUPITER - Primary Endpoint



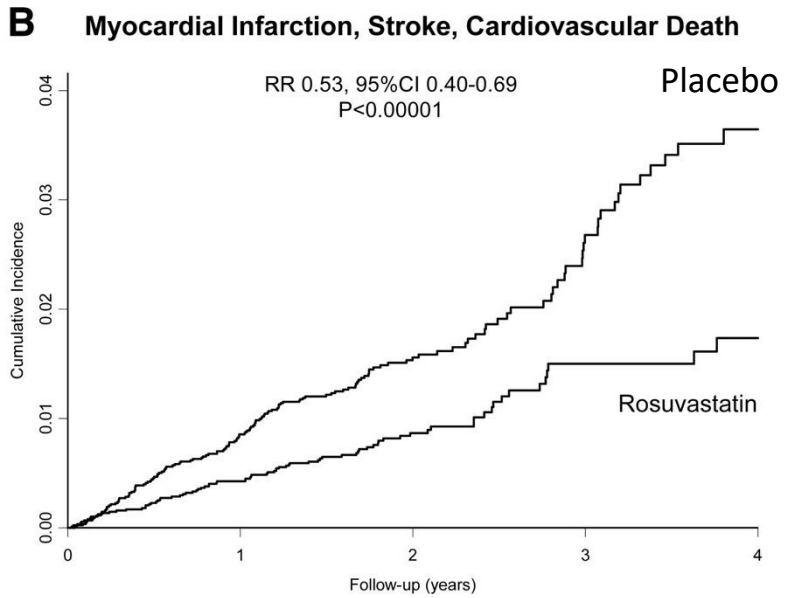
- Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

Ridker P *et al*. *N Eng J Med* 2008;359: 2195-2207

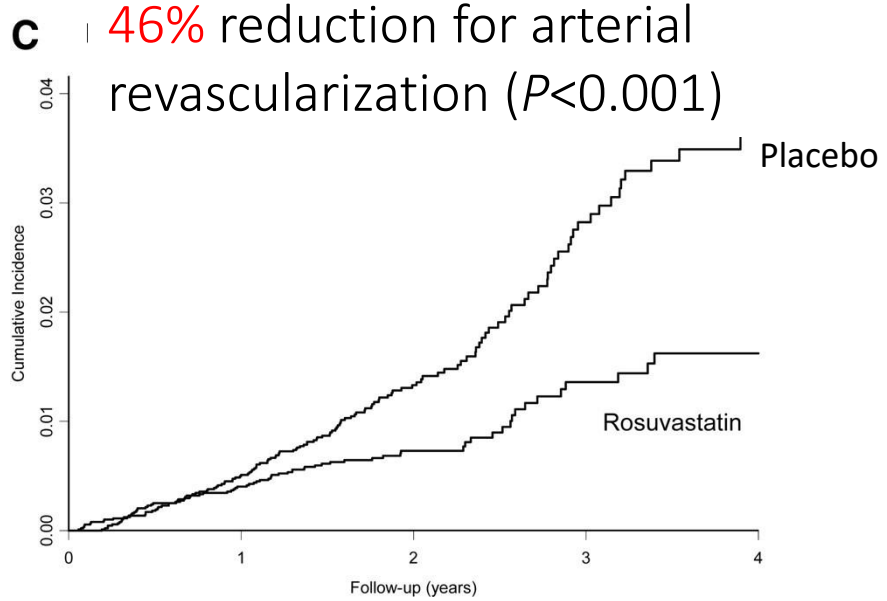
CRESTOR 20mg : Subgroup Results



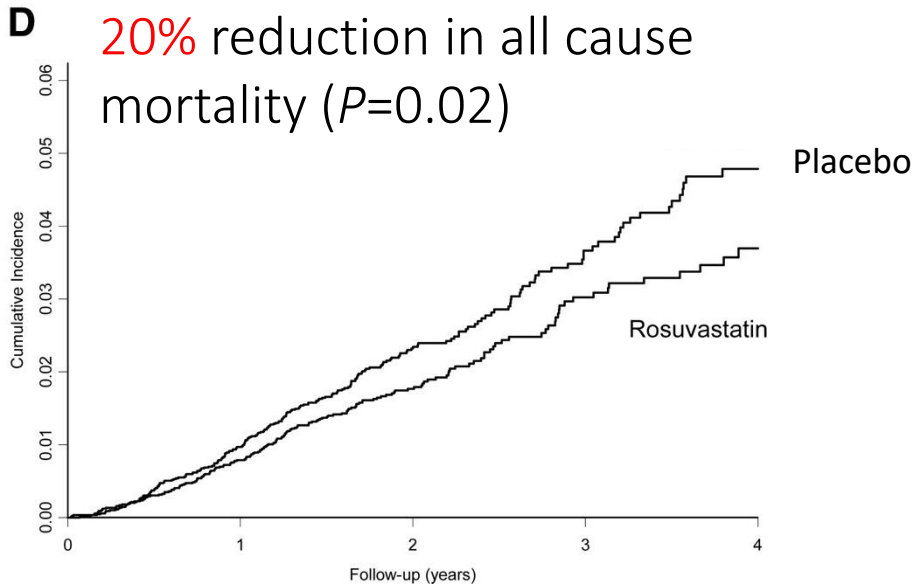
44% reduction of all vascular events (*P*<0.00001)



- 54% reduction in myocardial infarction (*P*=0.0002)
- 48% reduction in stroke (*P*=0.002)



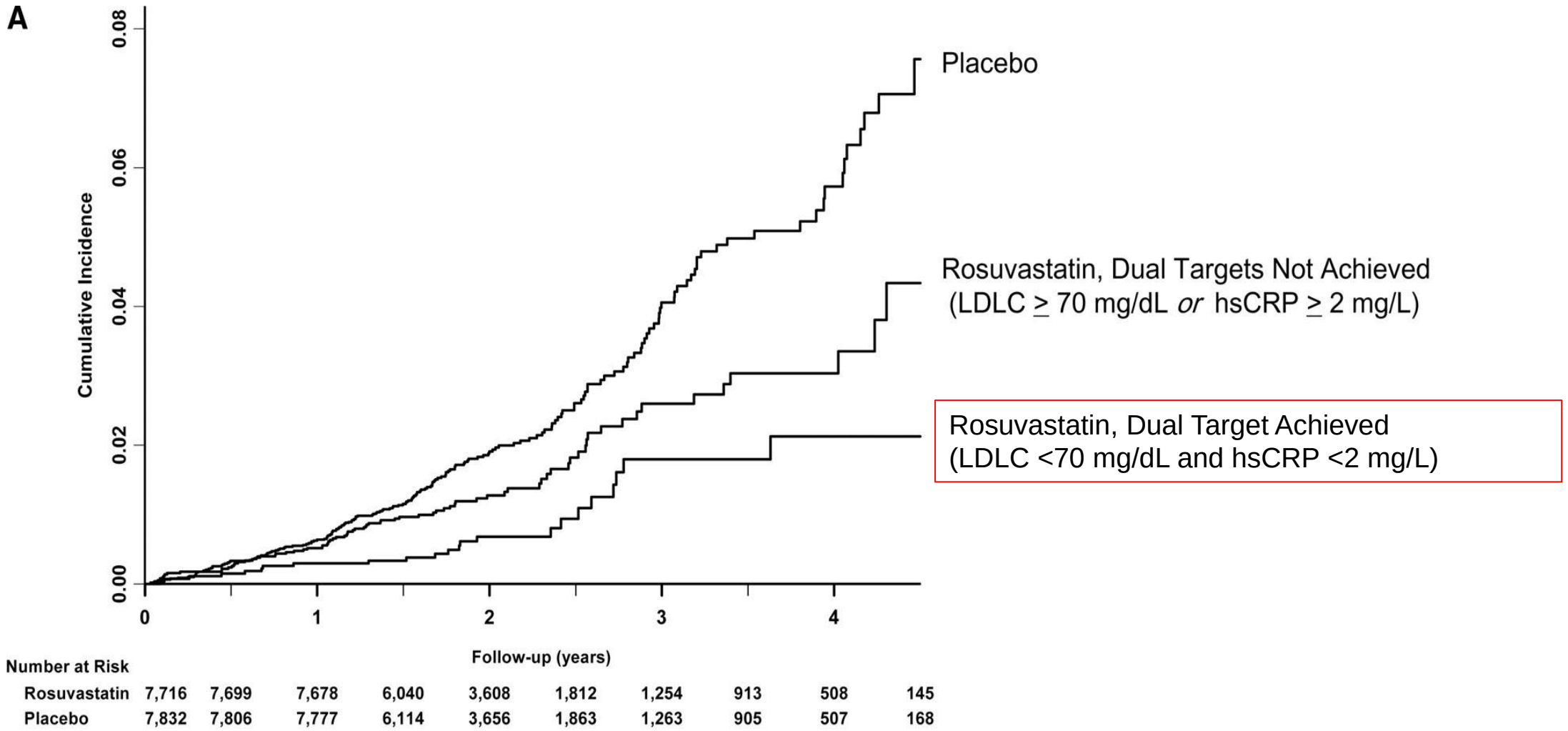
46% reduction for arterial revascularization (*P*<0.001)



20% reduction in all cause mortality (*P*=0.02)

Circ Cardiovasc Qual Outcomes. 2009 May;2(3):279-85.

CRESTOR 20mg : LDLC <70 mg/dL and hsCRP <2 mg/L



Circ Cardiovasc Qual Outcomes. 2009 May;2(3):279-85.

JUPITER Trial Conclusion

- In healthy men and women, no DM, no hypertension, LDL-C 130mg/dL, hsCRP>2mg/dL ⇒ rosuvastatin 20mg qd ⇒ both LDL-C ↓ *and* hsCRP ↓ ⇒ event-free survival ↑

JUPITER and It's Satellites

- In healthy men and women, hsCRP ↑ ⇒ rosuvastatin therapy ⇒ both LDLC *and* hsCRP ↓ ⇒ event-free survival ↑ **(N Engl J Med. 2008;359(21):2195-207)**

- Rosuvastatin therapy ⇒ Venous Thromboembolism ↓
  (Glynn et al NEJM 2009)

- Rosuvastatin therapy ⇒ Ischemia stroke↓ **(Circulation. 2010;121:143-150)**

- Rosuvastatin therapy ⇒ CKD p't 1st CV event and all cause mortality↓
  (J Am Coll Cardiol 2010;55:1266–73 5:1266–73)

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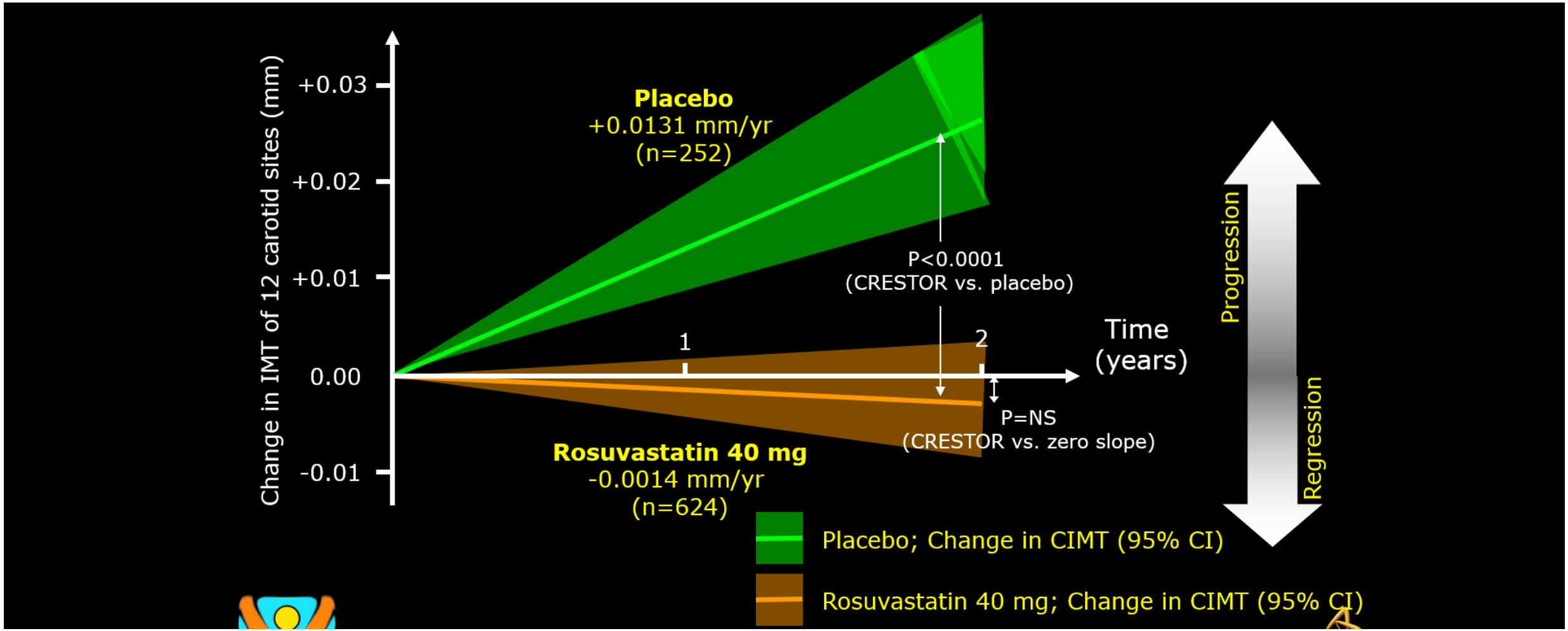
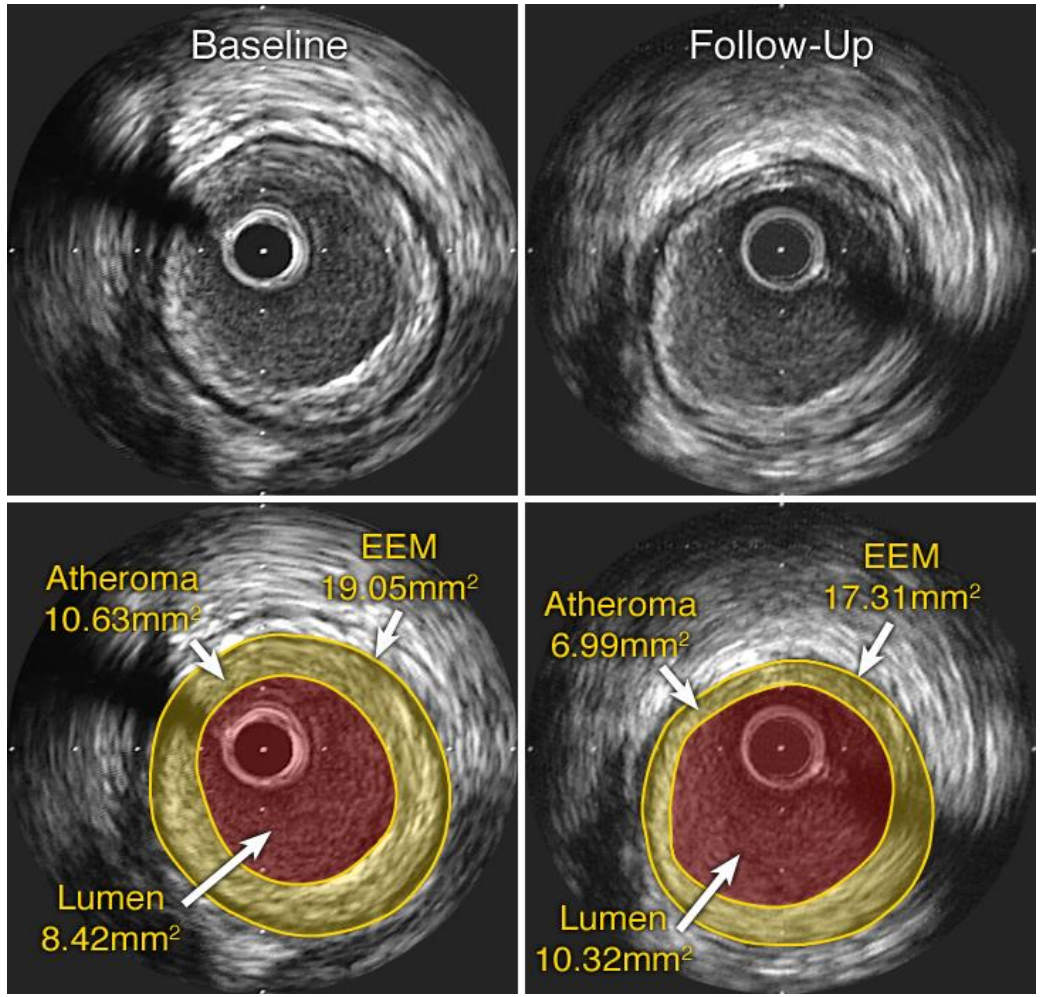
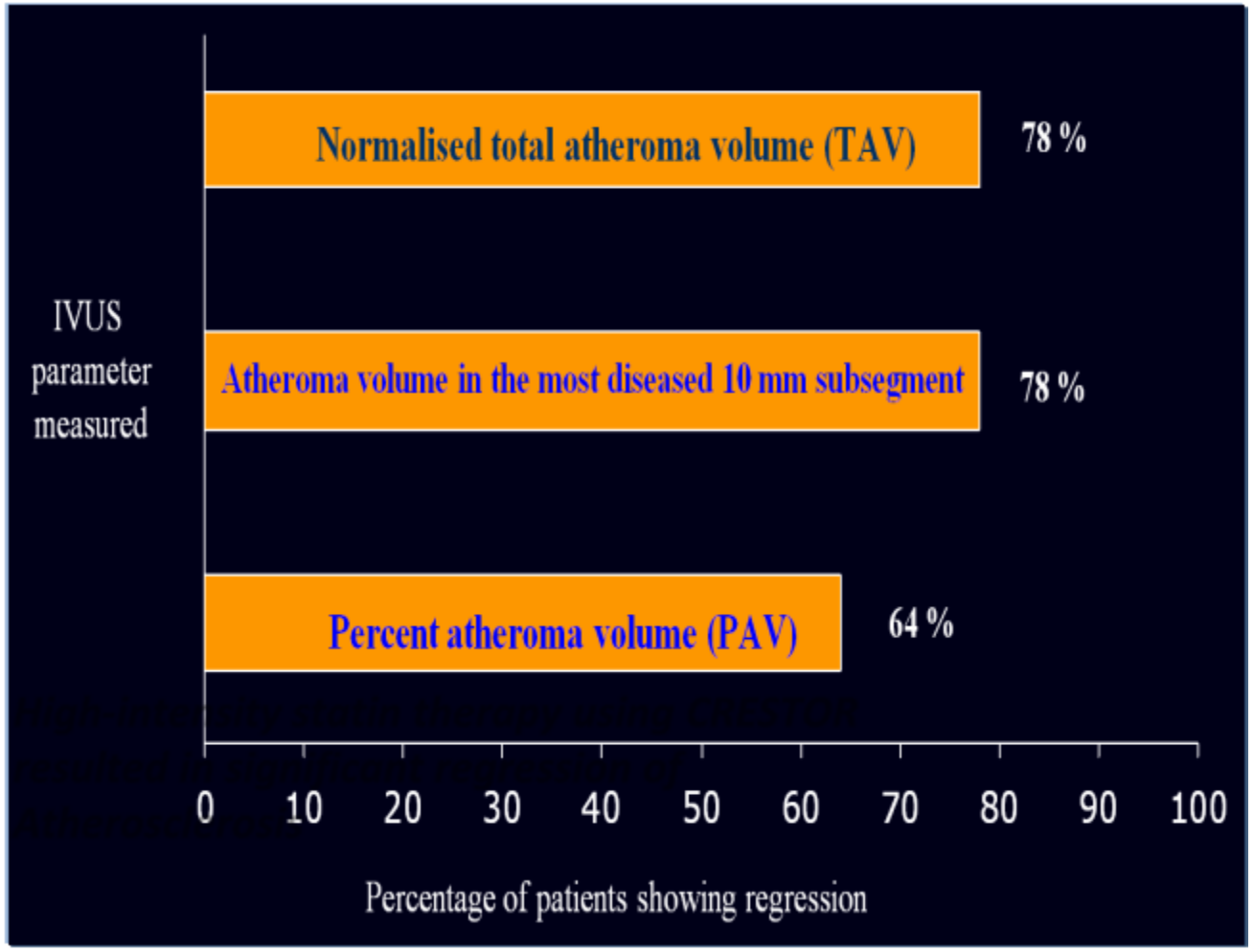
Carotid Sonography
METEOR primary endpoint: IMT result



Bots ML, *et al*. *Circulation 2007*;**116** (Suppl II): 17 (Abstract 194)

COSMOS study: Atheroma Regression in IVUS Study





Number(%) of patients showing regression measured by each IVUS parameter

Nissen et al; JAMA 2006; 296:1556, Pic.) Cleve Clin J Med, 2006; 73:937-944.

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- **Conclusions**

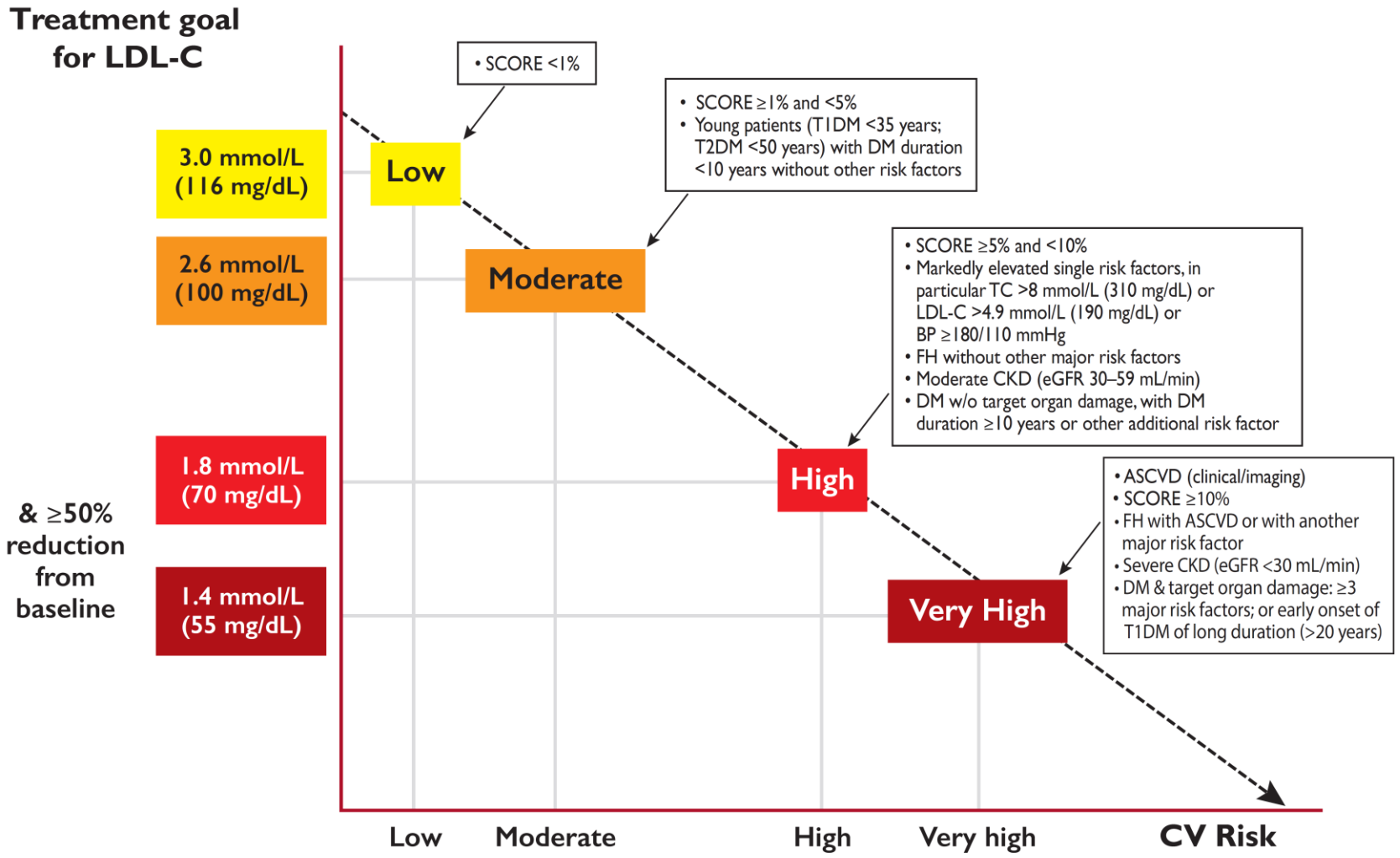
2019 ESC Guideline Key Massages

1. Cholesterol and risk ⇒ Lower is better ⇒ statin, ezetimibe, or PCSK9i ⇒absolute reduction in LDL-C 1mmole ⇒ ASCVD 20% ↓
2. High risk ASCVD ⇒ high potency statin ± PCSK9i ⇒ benefit !
3. CT coronary carter calcium score, ultrasound of carotid or femoral artery⇒ benefit !
4. ApoB ⇒ may be better in high TG, DM, obesity, or very low LDL-C.
5. Lp(a) ⇒ high inherited Lp(a) ⇒ ASCVD ↑↑

2019 ESC Guideline Key Massages

6. Intensify of treatment goals ⇒ very-high-risk p't LDL-C 50%↓ and <55 mg/dL
7. Recent ACS ⇒ highest tolerated statin + ezetimibe ⇒ LDL-C goal is not achieved at 4-6 weeks ⇒ add PCSK9i.
8. No known adverse effects of very low LDL-C ⇒ <1 mmol/L (38.6mg/dL)
9. Statin intolerance ⇒ myopathy ⇒ rare ⇒ changing statin or reducing dose ⇒ not to overwhelming risk of ASCVD
10. Older people ⇒ benefit in secondary prevention, primary prevention <75y/o ⇒ start from low dose, beware drugs interactions

2019 ESC Treatment Goal for LDL-C



European Heart Journal (2019) 00, 178

2019 健保給付 update

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
1.有急性冠狀動脈症候群病史 2. 曾接受心導管介入治療或外科冠動脈搭橋手術之冠狀動脈粥狀硬化患者(108/02/01)	與藥物治療可並行	LDL-C≧70mg/dL	LDL-C＜70mg/dL	第一年應每3-6個月抽血檢查一次，第二年以後應至少每6-12個月抽血檢查一次，同時請注意副作用之產生如肝功能異常，橫紋肌溶解症。
心血管疾病或糖尿病患者 (55mg/dL)	與藥物治療可並行	TC≧160mg/dL或 LDL-C≧100mg/dL	TC＜160mg/dL或 LDL-C＜100mg/dL	
2個危險因子或以上 (70mg/dL)	給藥前應有3-6個月非藥物治療	TC≧200mg/dL或 LDL-C≧130mg/dL	TC＜200mg/dL或 LDL-C＜130mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL或 LDL-C≧160mg/dL	TC＜240mg/dL或 LDL-C＜160mg/dL	
0個危險因子 (116mg/dL)	給藥前應有3-6個月非藥物治療	LDL-C≧190mg/dL	LDL-C＜190mg/dL	

102/08/01 移除字眼：如已達治療目標得考慮減量至最低有效劑量，並持續衛教

- 心血管疾病定義：
  (一)冠狀動脈粥狀硬化患者包含：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)
  (二)缺血型腦血管疾病患者包含：1.腦梗塞。2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）
- **危險因子定義： 1.高血壓2.男性≧45 歲，女性≧55 歲或停經者 3.有早發性冠心病家族史(男性≦55 歲，女性≦65 歲) 4.HDL-C<40mg/dL 5.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)。**

108年衛生福利部中央健康保險署

Rosuvastatin的劑量範圍是5-20 mg每天一次

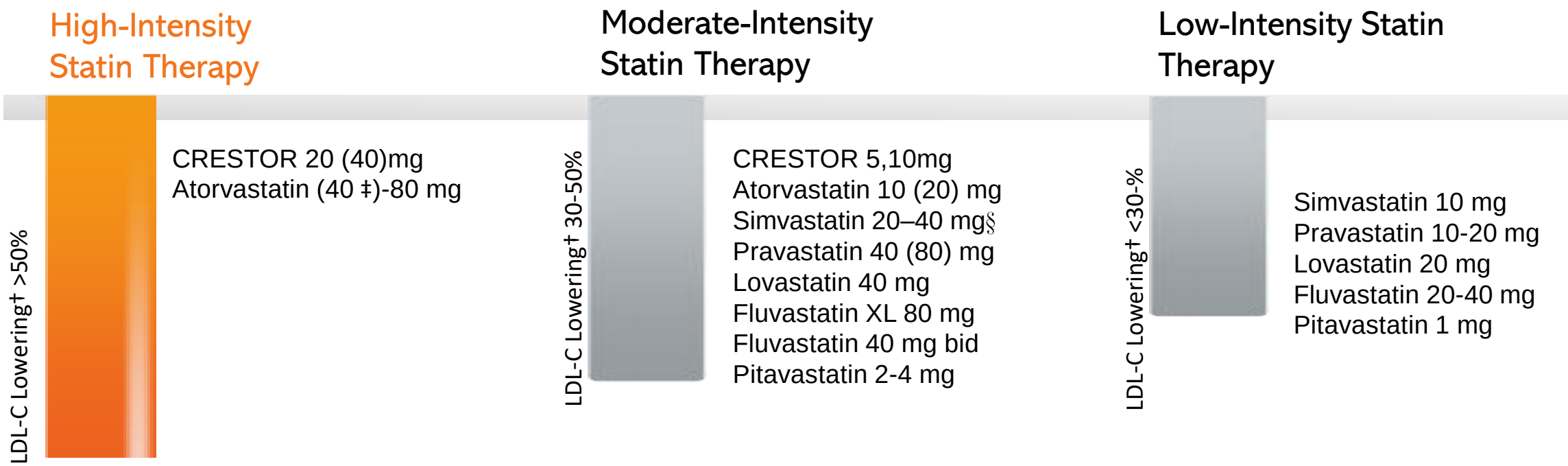
Take Home Massages

- Guidelines are not static documents but interactive pieces, that grow and build on one another.
- Rapidly evolving in atherosclerosis Tx
- New evidence ⇒ new guideline
- Strong evidence base, clear definition, easy to used, implemented into clinical practice

- ASCVD p't ⇒high potency statin⇒ before PCSK9i
- Rosuvastatin 10mg, 20mg is high potency, safe and effective (LDL-C lowering 47%, 55%)

Cardiovascular Center, TCVGH

High-intensity statin therapy for ASCVD prevention & treatment



Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the **VOYAGER** database
† LDL-C lowering that should occur with the dosage listed below each intensity
‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study
§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Rosuvastatin 40mg is not indicated in Taiwan”

Circulation. 2018 Nov 10:CIR0000000000000625