LIPITENSION

Introduction

- Cardiovascular diseases (CVDs) are a leading cause of death globally.

- Hypertension and Dyslipidemia are among the most important primary risk factors

Ruan Y et al. BMC Public Health. 2018; 18: 778.
Roth AG et al. J Am Coll Cardiol. 2017 Jul 4; 70(1): 1–25.

Hypertension and Dyslipidemia

- Hypertension is associated with an upregulation of lipid oxidation enzymes
- LDL, especially oxidized LDL, is a major cause of endothelial dysfunction
- The coexistence of dyslipidemic hypertension has been termed as 'LIPITENSION'
- For the ease of active identification, diagnosis, and management of these two risk factors together, as global CV risk factors
- Lipitension contributes to atherosclerosis and the resultant vascular risk

Dalal et al Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

Lipitension

- Dyslipidemia and hypertension are classical constituents of the metabolic syndrome
- The co-existence of the two risk factors has more than an additive adverse impact on the vascular endothelium, which results in enhanced atherosclerosis, leading to CVD

Yadav et al;Osong Public Health Res Perspect. 2014 Jun; 5(3): 169–175.
Dalal et al;Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

Dyslipidemia and hypertension

- Dyslipidemia and hypertension damage the endothelium,
  - triggering cell proliferation,
  - vascular remodelling, apoptosis, and increased cellular permeability
  - create a vicious cocktail of pathophysiological factors

Hurtubise J; Curr Atheroscler Rep. 2016 Dec;18(12):82

Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

NCEP-ATP III Guidelines

LIPITENSION

- Familial dyslipidemic hypertension was proposed as a genetic syndrome found in 12% of the patients with essential hypertension 48% of the hypertensive siblings.

- Insulin resistance coexists in up to 50% of the hypertensive individuals

Dalal et al;Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

LIPITENSION

- Studies have consistently indicated that hypertension and hypercholesterolemia frequently coexist, causing what is known as dyslipidemic hypertension

- The term LIPITENSION may help clinicians in easy identification and aggressive management of the two conditions together, ultimately preventing future cardiovascular events

Dalal et al;Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

Prevalence of Lipitension

- Overall prevalence of lipitension, hypertension alone, and hypercholesterolemia alone was 30, 47, and 18%, respectively.
- The prevalence of the co-existence of hypertension and dyslipidemia is in the range of 15–31%.
- The incidence of lipitension was 20% in women versus 16% in men ($p < 0.05$)
- The incidence was variable in different age groups with only 1.9% in the 20 – 39 year age group versus an increasing trend of 56% in the aged, > 80 years

Muthusamy et al; Management of dyslipidemia in hypertensionAbstracts 2016
Dalal et al;Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

Prevalence: Indian Scenario

- **Chennai Urban Population Study (CUPS study 5):** The highest prevalence of CAD (21.1%) was found in patients with multiple risk factors and these risk factors, in order, were diabetes, dyslipidemia, and hypertension

- Prevalence of the metabolic syndrome in a semi-urban south Indian was 30%.
  - Nearly 80% of these patients had systolic and 57% had diastolic hypertension, the dyslipidemia trend was high TG (38.8%) and low HDL (59%).

Dalal et al;Indian J Endocrinol Metab. 2012 Mar;16(2):240-5

Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline: Executive Summary

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Coexistence of Hypertension and Related Chronic Conditions

Table 5. CVD Risk Factors Common in Patients With Hypertension

Modifiable Risk Factors*	Relatively Fixed Risk Factors†
• Current cigarette smoking, secondhand smoking • Diabetes mellitus • Dyslipidemia/hypercholesterolemia • Overweight/obesity • Physical inactivity/low fitness • Unhealthy diet	• CKD • Family history • Increased age • Low socioeconomic/educational status • Male sex • Obstructive sleep apnea • Psychosocial stress

*Factors that can be changed and, if changed, may reduce CVD risk.
†Factors that are difficult to change (CKD, low socioeconomic/educational status, obstructive sleep apnea (3)), cannot be changed (family history, increased age, male sex), or, if changed through the use of current intervention techniques, may not reduce CVD risk (psychosocial stress) (3).
CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

New blood pressure targets and treatment recommendations

- For years, hypertension was classified as blood pressure (BP) reading of 140/90 mm Hg or higher.
- But the updated guideline classifies hypertension as a BP reading of **130/80 mm Hg or higher**.
- The updated guideline also provides new treatment recommendations, which include lifestyle changes as well as BP-lowering medications

2017 ACC/AHA Clinical Practice Guidelines . Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

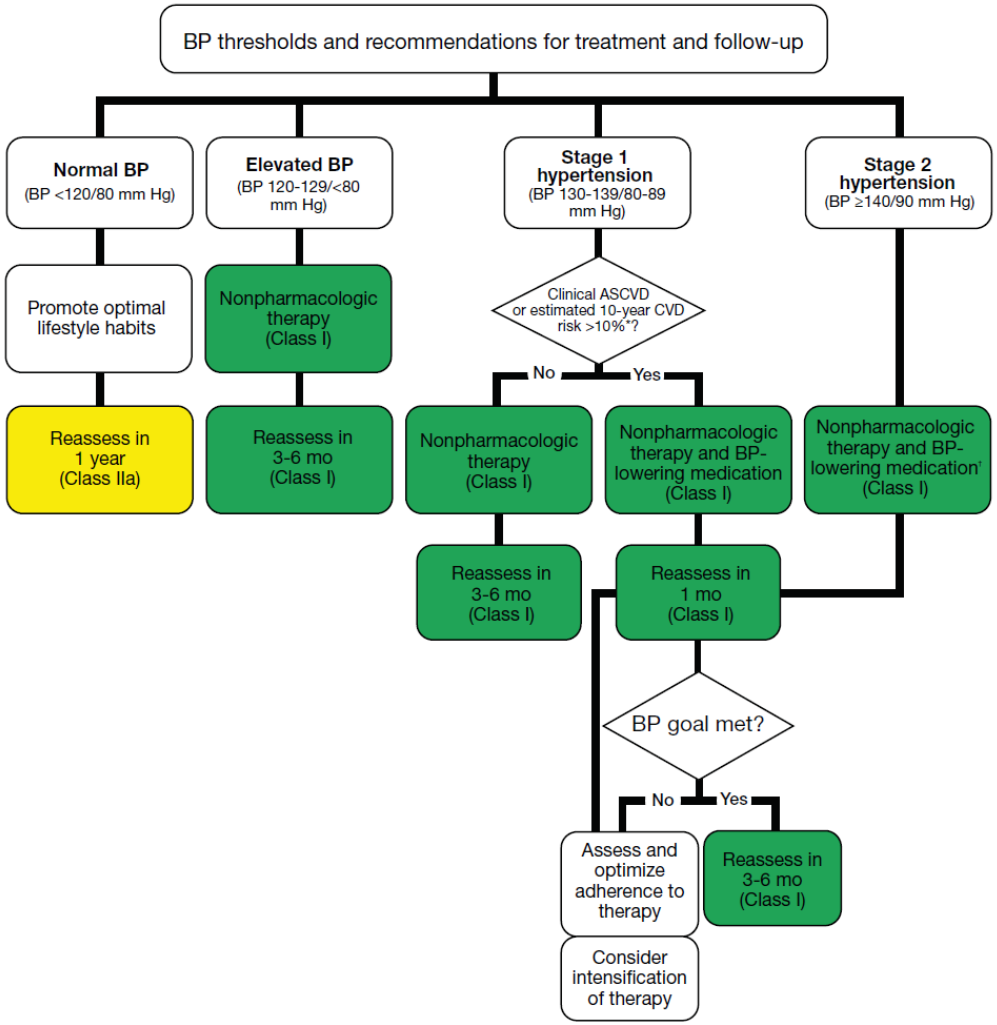
2017 ACC/ AHA Hypertension Guidelines

BP Category	Systolic BP		Diastolic BP	Treatment or Follow-up
Normal	<120 mm Hg	**and**	<80 mm Hg	Evaluate yearly; encourage healthy lifestyle changes to maintain normal BP
Elevated	120-129 mm Hg	**and**	<80 mm Hg	Recommend healthy lifestyle changes and reassess in 3-6 months
Hypertension: stage 1	130-139 mm Hg	**or**	80-89 mm Hg	Assess the 10-year risk for heart disease and stroke using the atherosclerotic cardiovascular disease (ASCVD) risk calculator • If risk is less than 10%, start with healthy lifestyle recommendations and reassess in 3-6 months • If risk is greater than 10% or the patient has known clinical cardiovascular disease (CVD), diabetes mellitus, or chronic kidney disease, recommend lifestyle changes and BP-lowering medication (1 medication); reassess in 1 month for effectiveness of medication therapy – If goal is met after 1 month, reassess in 3-6 months – If goal is not met after 1 month, consider different medication or titration – Continue monthly follow-up until control is achieved
Hypertension: stage 2	≥140 mm Hg	**or**	≥90 mm Hg	Recommend healthy lifestyle changes and BP-lowering medication (2 medications of different classes); reassess in 1 month for effectiveness • If goal is met after 1 month, reassess in 3-6 months • If goal is not met after 1 month, consider different medications or titration • Continue monthly follow-up until control is achieved

ACC/AHA Clinical Practice Guidelines. Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

2017 ACC/ AHA Hypertension Guidelines

BP thresholds and recommendations for treatment and follow-up.



ACC/AHA Clinical Practice Guidelines . Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

2017 ACC/ AHA Hypertension Guidelines

BP thresholds and recommendations for treatment and follow-up.

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ACC/AHA Clinical Practice Guidelines . Whelton PK et al. Hypertension. 2017 Nov 13. pii: HYP.0000000000000066

NCEP-ATP III Guidelines

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Measurements of LDL-C and Non–HDL-C

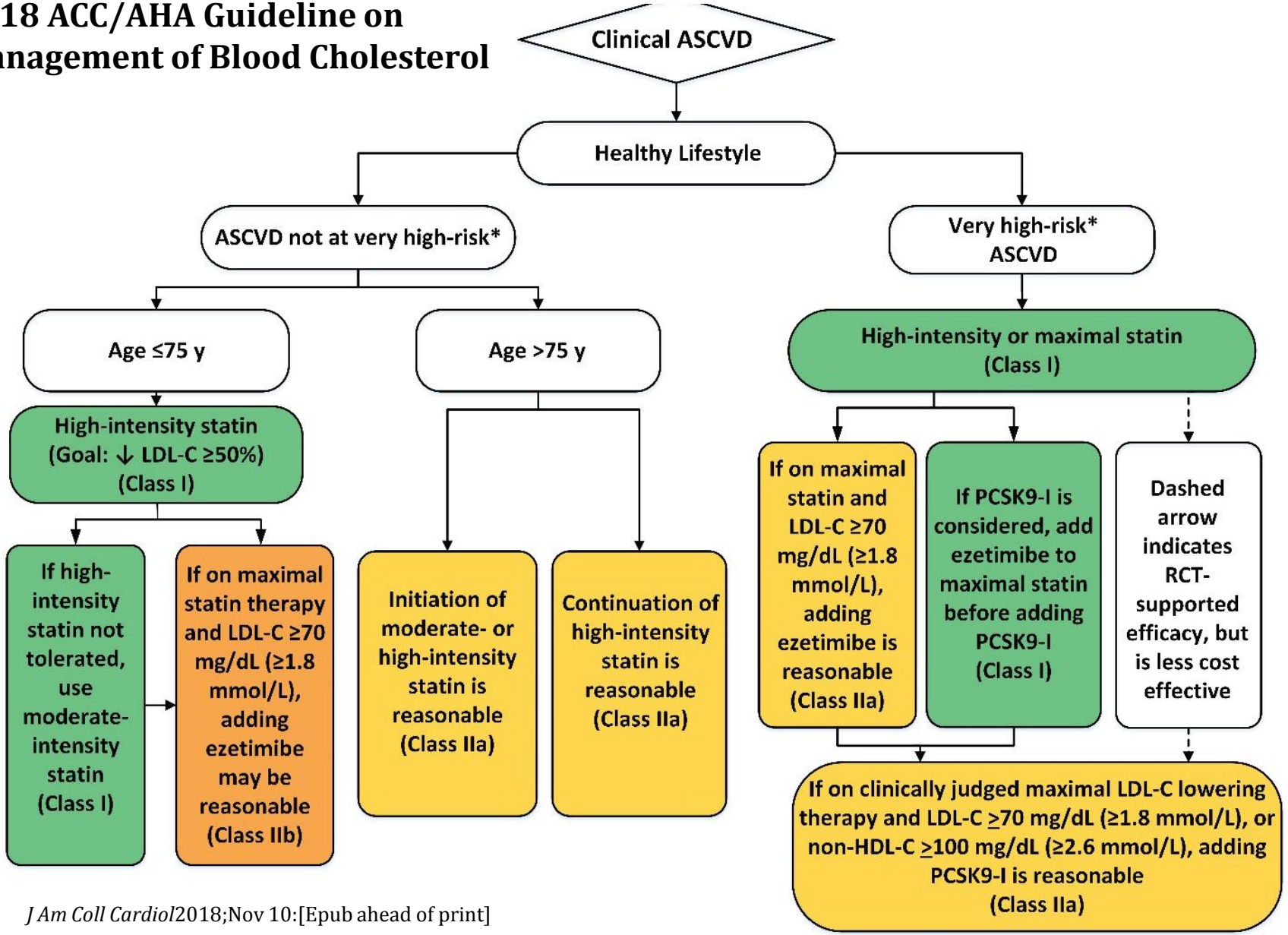
Referenced studies that support recommendations are summarized in Online Data Supplement 1.

COR	LOE	Recommendations
I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.1-1–S2.1-6).
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.1-1–S2.1-4).
IIa	C-LD	3. For patients with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula (S2.1-7–S2.1-9).
IIa	C-LD	4. In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.

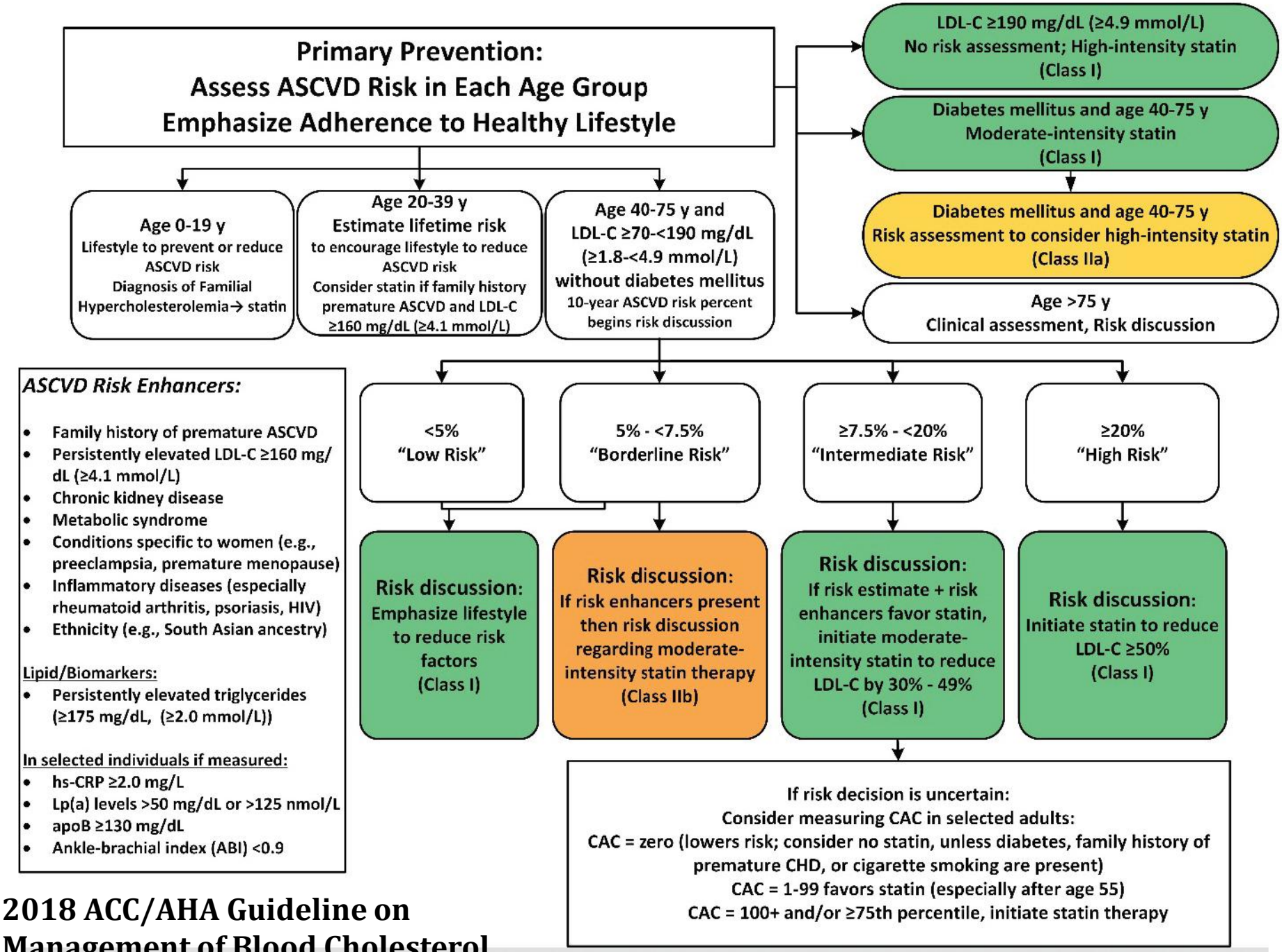
*J Am Coll Cardiol*2018;Nov 10:[Epub ahead of print]

Secondary Prevention in Patients With Clinical ASCVD

2018 ACC/AHA Guideline on Management of Blood Cholesterol



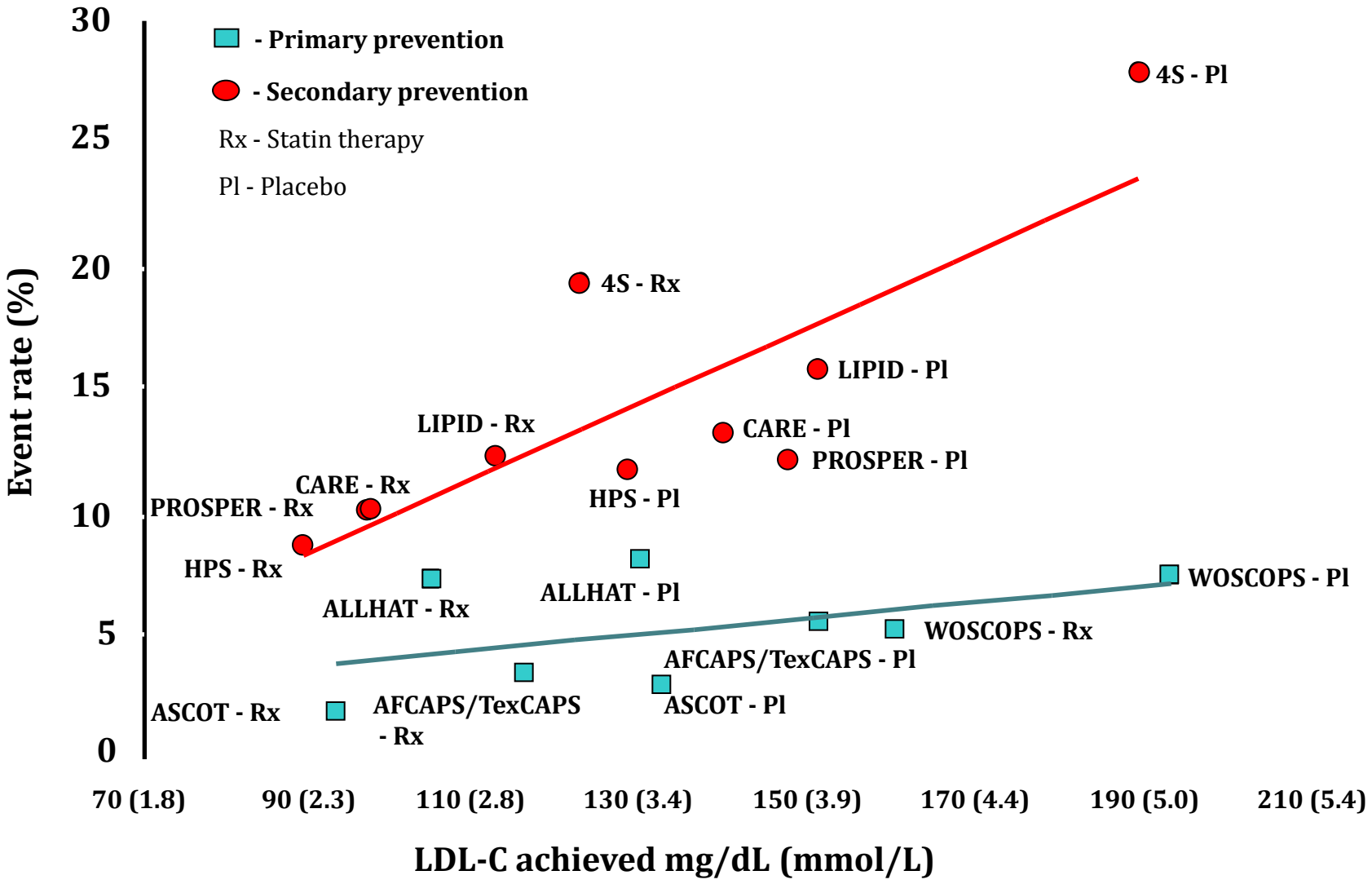
*J Am Coll Cardiol*2018;Nov 10:[Epub ahead of print]



2018 ACC/AHA Guideline on Management of Blood Cholesterol

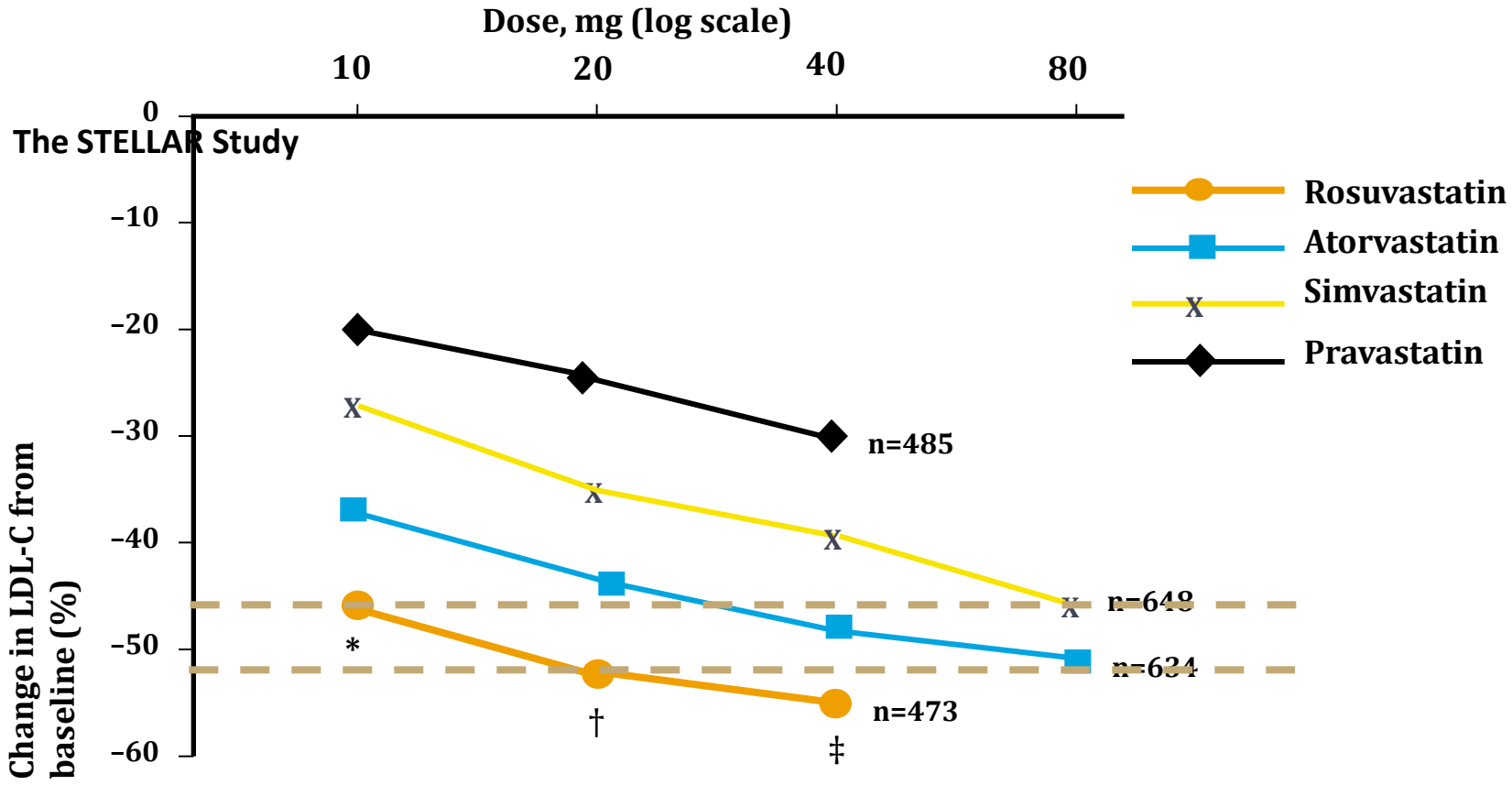
Key Studies

Relationship between LDL-C and CV Event Rate



Jones PH et al. *Am J Cardiol* 2003;92:152–160

Rosuvastatin versus Comparators: LDL-C Efficacy Across the Dose Range

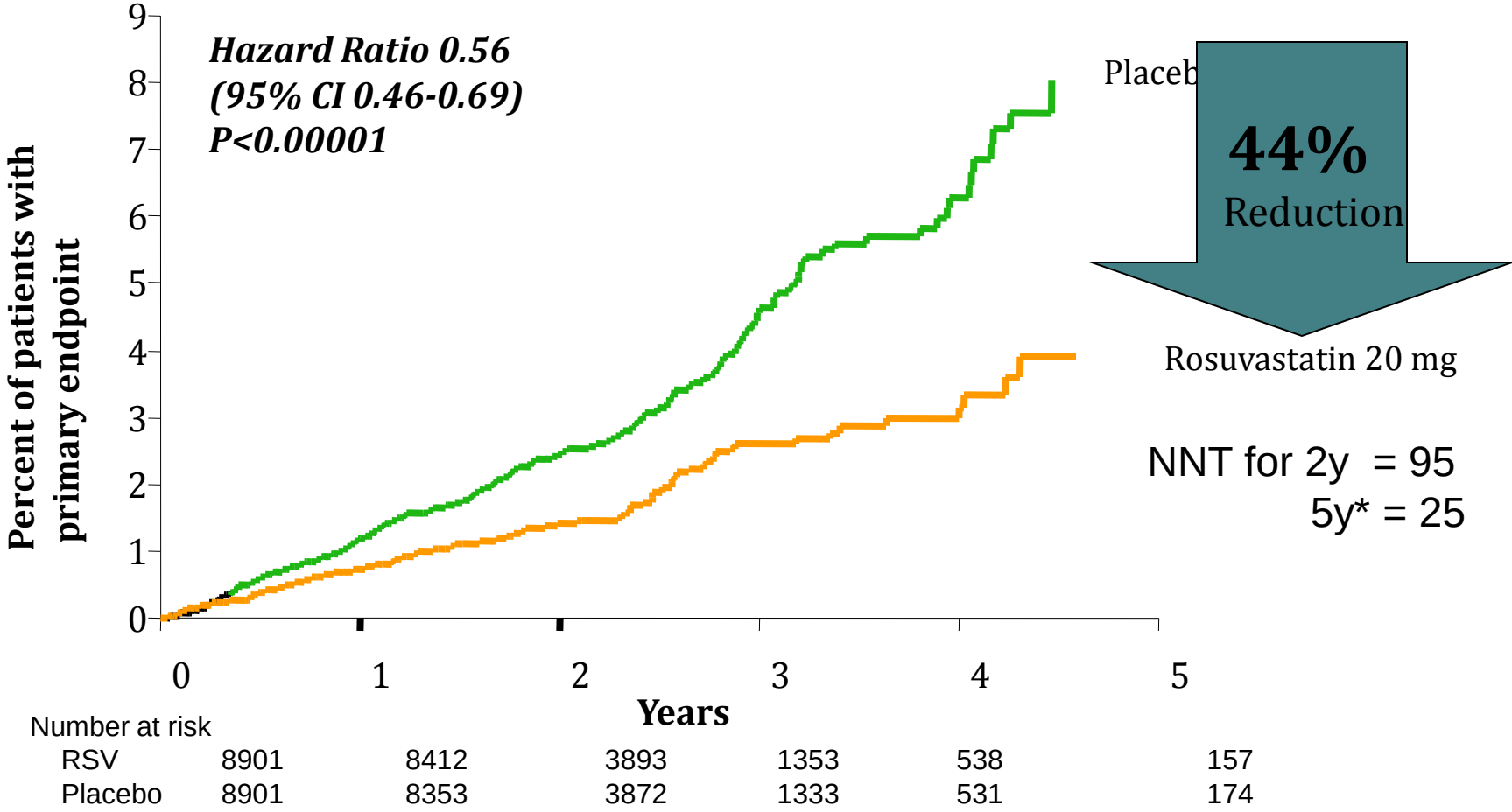


*p<0.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg
†p<0.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg
‡p<0.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg

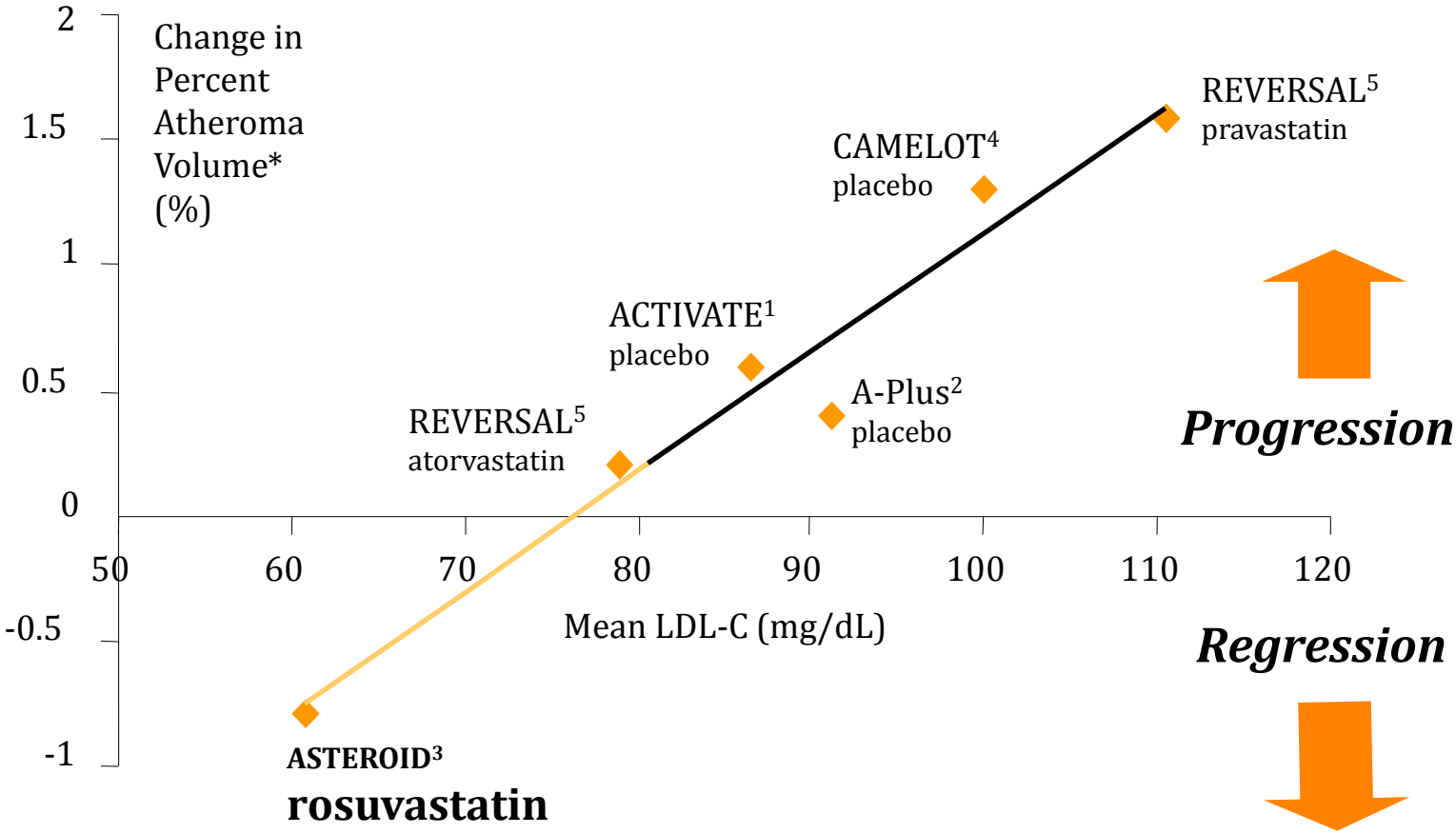
Jones PH et al. *Am J Cardiol* 2003;92:152–160c

JUPITER – Study Results

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

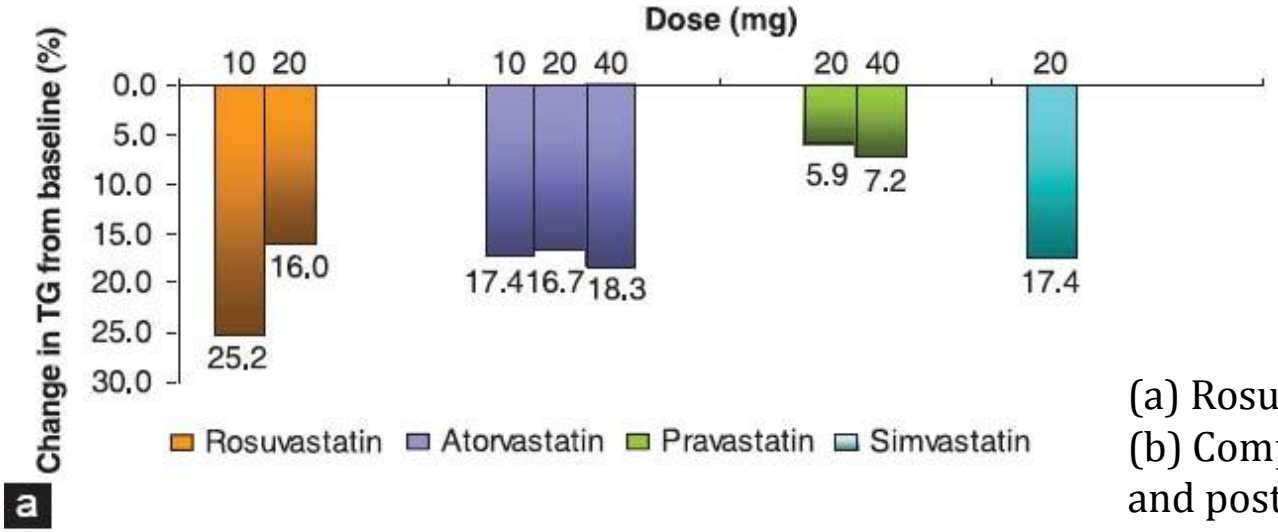


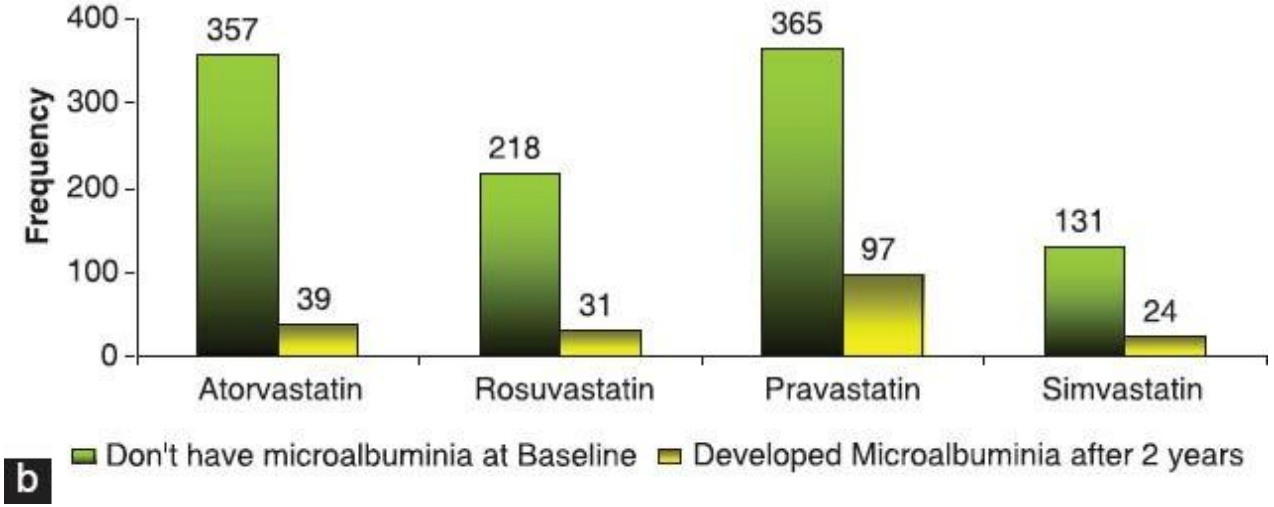
The relationship between mean LDL-C and change in percent atheroma volume (PAV) in IVUS studies†



1 Nissen S et al. N Engl J Med 2006;354:1253-1263. **2** Tardif J et al. Circulation 2004;110:3372-3377.
3 Nissen S et al. JAMA 2006;295 (13):1556-1565 **4** Nissen S et al. JAMA 2004;292: 2217–2225.
5 Nissen S et al. JAMA 2004; 291:1071–1080

Comparison of various statins





(a) Rosuvastatin versus other statins, (b) Comparison of patients with pre- and posttreatment microalbuminuria at the end of 2 years

Bener A et al. Indian J Pharmacol. 2014 Jan-Feb; 46(1): 88–93

New evidence from ASCOT-LLA

- The data suggests that there is *no evidence for increased AEs associated with the use of statins.*

- The reported excess of muscle-related AEs, in observational studies, is possibly due to confounding by knowledge of the use of statins among patients and physicians alike, and compounded by the widespread adverse media publicity – The “Nocebo” effect.

- Apparent beneficial effects on sleep disturbance, and possibly on erectile dysfunction, with the use of statins need to be confirmed in other studies.

(ASCOT-LLA)- Lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial

JOURNAL OF THE ASSOCIATION OF PHYSICIANS OF INDIA • OCTOBER 2013 • VOL. 61

ORIGINAL ARTICLE

Efficacy of Rosuvastatin in Achieving Target HDL, LDL, Triglycerides and Total Cholesterol Levels in Type 2 Diabetes Mellitus (T2DM) with Newly Diagnosed Dyslipidaemia: An Open Label, Nonrandomised, Non-Interventional and Observational Study in India

Siddharth N Shah[1], Jaspal Arneja[2]

- Open label, nonrandomised, non-interventional, observational study in India involving T2DM patients who require statin therapy to control dyslipidaemia patients (N=4369)

- Data were collected at baseline, interim (8 weeks) and subsequently at 16 weeks of Rosuvastatin (10 and 20 mg) therapy

Shah et al; J Assoc Physicians India. 2013 Oct;61(10):721-6, 732

Results

Table 2: Mean Change in Low-density lipoprotein Cholesterol Level after treatment for 16 weeks

*Frequency of LDL-C Levels		Gender (Mean and S.D. Values)			
		Female		Male	
	Frequency (%)	LDL Levels mg/dl (at 16 weeks)	% Change in LDL Levels	LDL Levels in mg/dl (at 16 weeks)	% Change in LDL Levels
LDL Levels					
<100	1115(25.52%)	-45.94(38.19)	-36.1%	-44.17(38.58)	-35.6%
100-129	1559(35.68%)	-38.53(35.36)	-25.0%	-57.15(554.02)	-33.2%
130-159	1144(26.18%)	-27.54(56.30)	-16.3%	-25.22(25.29)	-15.1%
160-189	433(9.91%)	-14.47(27.59)	-7.94%	-17.39(27.22)	-9.28%
≥190	118(2.70%)	114.89(282.06)	56.13%	-7.43(97.53)	-3.2%
		Target Achievement			
		Female		Male	Total
Achieved		851 (19.48%)		1823 (41.73%)	2674 (61.20%)
Not Achieved		542 (12.41%)		1153 (26.39%)	1695 (38.80%)

LDL-C: Low-density lipoprotein Cholesterol; *NCEP ATP III Guidelines

Shah et al; J Assoc Physicians India. 2013 Oct;61(10):721-6, 732

Overall 63.95% of patients had achieved the total cholesterol target and 50.06% achieved triglyceride target

Table 4: Mean change in total cholesterol level after treatment for 16 weeks

	Frequency of Total Cholesterol* Levels		Gender (Mean and S.D. Values)			
			Female		Male	
TC Levels		Frequency (%)	TC Levels in mg/dl (at 16 weeks)	% Change in TC Levels	TC Levels in mg/dl (at 16 weeks)	% Change in TC Levels
	<200	2794(63.95%)	-51.20(46.26)	-23.2%	-56.10(71.35)	-24.9%
	200-239	1097(25.11%)	-36.31(41.50)	-14.6%	-37.03(35.32)	-14.8%
	≥240	478(10.94%)	-43.89(95.21)	-13.5%	-30.85(54.64)	-10.3%

Target Achievement	Female	Male	Total
Achieved	910 (20.83%)	1884 (43.12%)	2794 (63.95%)
Not Achieved	483 (11.06%)	1092 (24.99%)	1575 (36.05%)

TC: Total Cholesterol; *NCEP ATP III Guidelines

<u>Conclusion:</u> Rosuvastatin safely and beneficially alters the entire spectrum of lipoproteins in Indian patients

Shah et al; J Assoc Physicians India. 2013 Oct;61(10):721-6, 732

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International Journal of Recent Advances in Multidisciplinary Research

Vol. 04, Issue 10, pp.2836-2840, October, 2017

2017

RESEARCH ARTICLE

ANTIHYPERTENSIVE EFFECT OF ROSUVASTATIN IN NORMOCHOLESTEROLEMIC HYPERTENSIVE PATIENTS AND ITS ASSOCIATION WITH FLOW MEDIATED DILATION AND OXIDATIVE STRESS

*[1]Abha Sharma and [2]RajnishAvasthi

- **Objective:**To study the effect of rosuvastatin therapy in normocholesterolemic patients when added to antihypertensive agent on
  - (a) Blood pressure in stage 1 hypertensive individuals.
  - (b) Endothelial function and oxidative stress levels in stage 1 hypertensive individuals
- **Randomised double blind study**

- **Conclusion:** Addition of rosuvastatin in normocholesterolemic subjects who are already on antihypertensive treatment lead to significant fall in mean systolic blood pressure and mean pulse pressure

- Rosuvastatin causes improvement of antioxidant level and endothelial function

- **This study reinforces relatively poorly understood and under-reported hypotensive potential of statin, one of many pleiotropic effect associated with the class of statin.**

Sharma et al; Oct 2017(4)10,2836-2840

TCP Transl Clin Pharmacol
2016;24(3):132-136
http://dx.doi.org/10.12793/tcp.2016.24.3.132

Blood pressure lowering effect of statin drugs with an application to rosuvastatin

Young-A Heo[1,2], Mijeong Son[1,2] and Kyungsoo Park[1]*
[1]Department of Pharmacology, Yonsei University College of Medicine, Seoul 03722, Korea, [2]Brain Korea 21 Plus Project for Medical Science, Yonsei University, Seoul 03722, Korea
*Correspondence: K. S. Park; Tel: +82-2-2228-1735, Fax: +82-2-313-1894, E-mail: kspark@yuhs.ac

- This study aimed to investigate the potential role of rosuvastatin in BP lowering properties in Korean population
- Data were taken from three randomized, multiple-dose cross over studies

Heo et al; Transl Clin Pharmacol2016;24(3):132-136

Table 1. Characteristics of clinical trials included in the analysis

Study, Design	Subjects (no. of subjects)	Dosage per day	Duration of study	BP sampling Schedule
Randomized, open-label, 3-period, multiple-dose crossover study[13]	Healthy normotensive male subjects[35]	20 mg	7 days	At predose on days 1 through 6 and at 0, 2, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 7
Randomized, open-label, 2-part, 2-period, multiple-dose crossover study[14]	Healthy normotensive male subjects[23]	20 mg	6 days	At predose on days 1 through 5 and at 0, 2, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 6
Randomized, open-label, 6-sequence, 3-period, multiple-dose crossover study[12]	Healthy normotensive male subjects[33]	10 mg	5 days	At predose on days 1 through 4 and at 0, 4, 8, 12, 24, 48 and 72 hours after the last dose on day 5

Rosuvastatin monotherapy may produce small blood pressure lowing effect in DBP.

Heo et al; Transl Clin Pharmacol2016;24(3):132-136

ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)

- Goal: To test whether Telmisartan was similarly effective to Ramipril
- Population and treatment: 25 620 patients ≥ 55 years of age with CHD or diabetes plus additional risk factors without evidence of HF.
- Randomized to ramipril 10 mg/day, telmisartan 80 mg/day, or combination of the two for a mean duration of 55 months.
- Primary outcome: A composite of CV death, MI, stroke, or hospitalization for HF

N Engl J Med 2008; 358:1547-1559

ONTARGET: Results

- Telmisartan was shown to be noninferior to ramipril

Key results

Outcome	Ramipril (n=8576), %	Telmisartan (n=8542), %	Combination (n=8502), %	Risk ratio (95% CI)[a]	Risk ratio (95% CI)[b]
Primary end point	16.5	16.7	16.3	1.01 (0.94–1.09)	0.99 (0.92–1.07)
CV death/MI/stroke	14.1	13.9	14.1	0.99 (0.91–1.07)	1.00 (0.93–1.09)
MI	4.8	5.2	5.2	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke	4.7	4.3	4.4	0.91 (0.79–1.05)	0.93 (0.81–1.07)
CHF hospitalization	4.1	4.6	3.9	1.12 (0.97-1.29)	0.95 (0.82– 1.10)
CV death	7.0	7.0	7.3	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Any death	11.8	11.6	12.5	0.98 (0.90–1.07)	1.07 (0.98–1.16)
Renal impairment	10.2	10.6	13.5	1.04 (0.96–1.14)	1.33 (1.22–1.44)

N Engl J Med 2008; 358:1547-1559

Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND)

- Goal: To assess whether telmisartan would be effective in patients intolerant to ACE inhibitors with CV disease or diabetes with end-organ damage

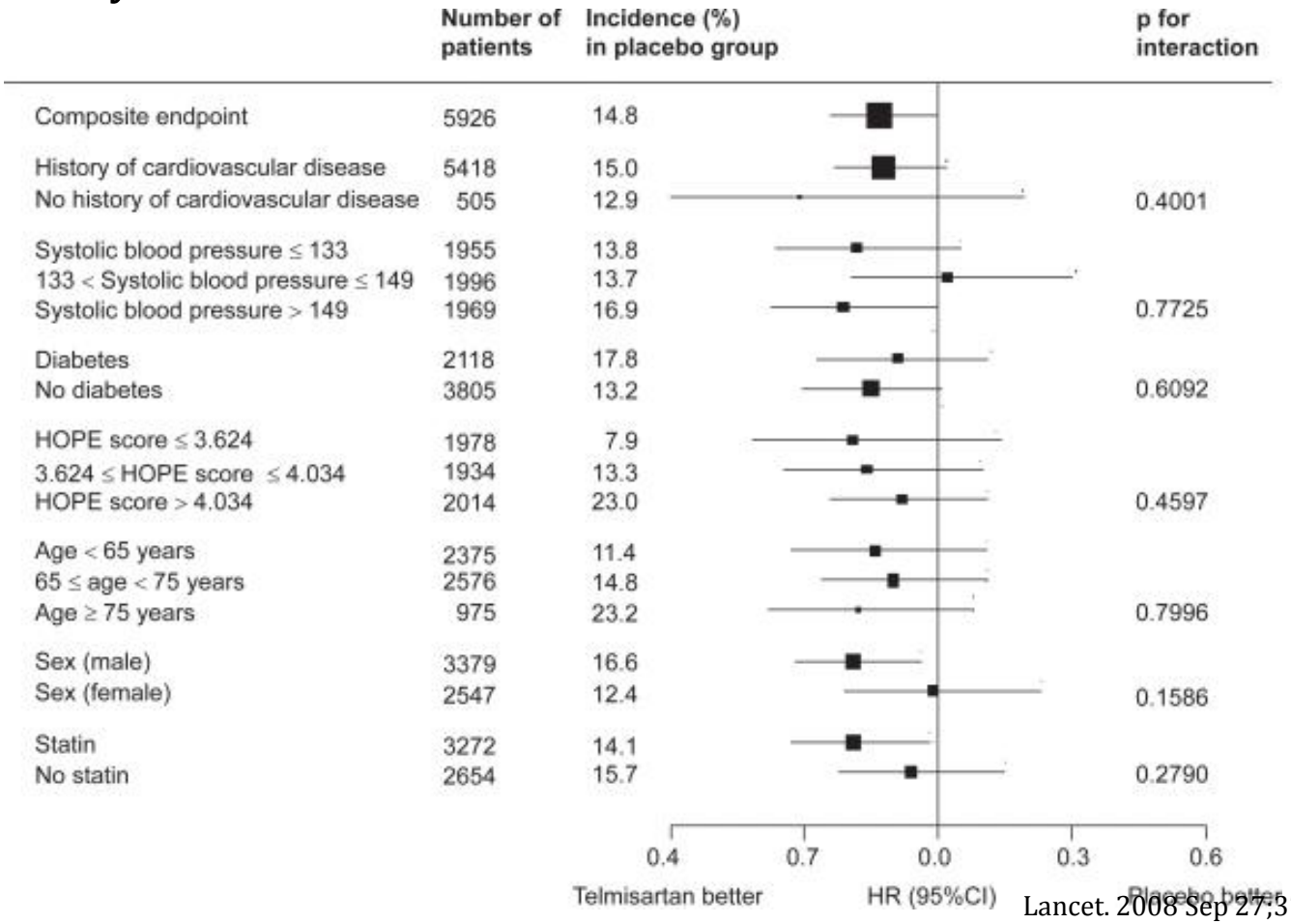
- 5926 patients were randomised to receive telmisartan 80 mg/day (n=2954) or placebo (n=2972)

- The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalisation for heart failure.

Lancet. 2008 Sep 27;372(9644):1174-83

TRANSCEND Results

- Mean blood pressure was lower in telmisartan group than in placebo group
- Telmisartan had an impact on the composite outcome of cardiovascular death, myocardial infarction, or stroke.



Lancet. 2008 Sep 27;372(9644):1174-83

PROTECTION Program

- The objective of the Programme of Research tO show Telmisartan End-organ proteCTION (PROTECTION) is to measure the end-organ protective effects of telmisartan in patients at high risk of renal, cardiac and vascular damage.

- Nine clinical studies will examine the effects of telmisartan in about 5000 hypertensive patients with
  - isolated systolic hypertension,
  - type 2 diabetes,
  - obesity,
  - left ventricular hypertrophy or
  - renal disease.

- The programme also investigated the effects of an ARB on key surrogate markers of organ tissue damage.

Weber M et al . J Hypertens Suppl. 2003 Jul;21(6):S37-46.

PROTECTION

Programme of Research tO show Telmisartan End-organ proteCTION

10 clinical Studies in > 6500 Patients from 32 countries

PRISMA I & II
EMBPS

Telmisartan vs. Ramipril

TRENDY
Dysfunction of the renal endothelium

Telmisartan vs. Ramipril

ARBs FDC
Morning surge in BP

Telmisartan + HCTZ
vs. Losartan + HCTZ

INNOVATION
Diabetic Nephropathy

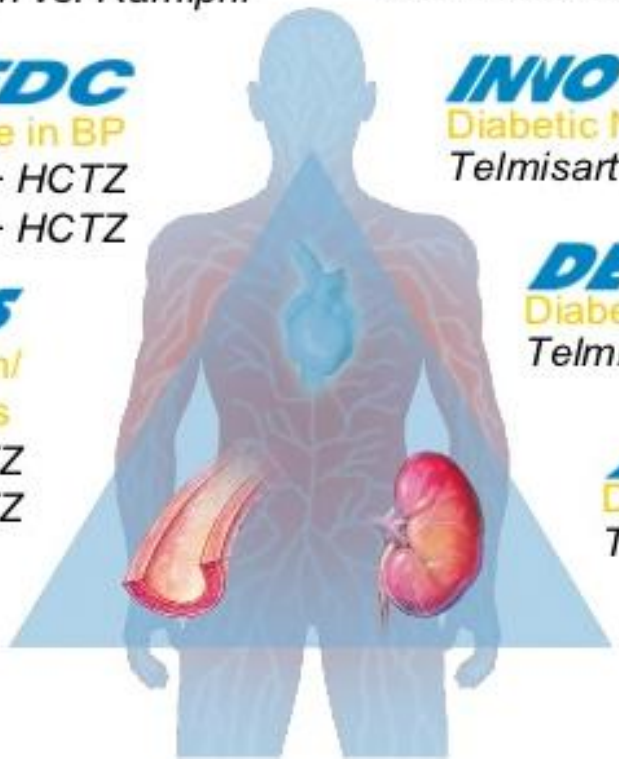
Telmisartan vs. Placebo

ATHOS
Systolic Hypertension/
elderly hypetensives

Telmisartan + HCTZ
vs. Amlodipine + HCTZ

DETAIL
Diabetic Nephropathy

Telmisartan vs. Enalapril



AMADEO
Diabetic Nephropathy

Telmisartan vs. Losartan

SMOOTH
Diabetes + Overweight

Telmisartan + HCTZ
vs. Valsartan + HCTZ

VIVALDI
Diabetic Nephropathy

Telmisartan vs. Valsartan

Weber M et al . J Hypertens Suppl. 2003 Jul;21(6):S37-46.

Table 1 Summary of telmisartan clinical trials

Study	Number of patients	Patient population	Duration	Primary end points	Intervention	Main outcomes
PRISMA I, II	1613	Hypertension	14 weeks	Change from baseline in mean ambulatory systolic BP and diastolic BP during the final 6 hours of the 24-hour dosing cycle	Telmisartan 80 mg/day vs ramipril 5 or 10 mg/day	Telmisartan is more effective than ramipril throughout the 24-hour period and during the early morning
DETAIL	250	Type 2 diabetes + hypertension + early diabetic nephropathy	5.0 years	Change in glomerular filtration rate	Telmisartan 80 mg/day vs enalapril 20 mg/day	Telmisartan is not inferior to enalapril in providing long-term renoprotection in persons with type 2 diabetes (change in glomerular filtration rate for telmisartan –17.9 mL per minute per 1.73 m^2, –14.9 mL per minute per 1.73 m^2 for enalapril; treatment difference –3.0 mL per minute per 1.73 m^2 95% CI: –7.6 to 1.6 mL per minute per 1.73 m^2)
INNOVATION	527	Type 2 diabetes + microalbuminuria (Japanese)	1.3 years	Transition rate from incipient to overt nephropathy	Telmisartan 80 mg/day vs telmisartan 40 mg/day vs placebo	Telmisartan reduced transition from incipient to overt nephropathy (16.7% telmisartan 80 mg, 22.6% telmisartan 40 mg, 49.9% placebo; both telmisartan doses vs placebo, $P < 0.0001$)
VIVALDI	885	Type 2 diabetes + hypertension + overt nephropathy	1 year	Change from baseline in the 24-hour proteinuria	Telmisartan 80 mg/day vs valsartan 160 mg/day	Similar reduction 33% with both telmisartan and valsartan
AMADEO	860	Type 2 diabetes + hypertension + overt nephropathy	1 year	Difference in the urinary albumin to creatinine ratio	Telmisartan 80 mg/day vs losartan 100 mg/day	Reduction significantly better with telmisartan 29.8% vs losartan 21.4% ($P < 0.031$)
ONTARGET	25,620	Coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	4.7 years	Composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure	Telmisartan 80 mg/day vs ramipril 10 mg/day vs combination	Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes (RR: 1.01; 95% CI: 0.94–1.09)
TRANSCEND	5926	Intolerance to ACE inhibitors + coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage	4.7 years	Composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure	Telmisartan 80 mg/day vs placebo	Telmisartan did not reduce composite of four cardiovascular outcomes in high risk patients with intolerance to ACE inhibitors (HR: 0.92; 95% CI: 0.81–1.05; $P = 0.216$)

Akhrass et al;Vascular Health and Risk Management 2011:7 677–683

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Mixed–effects analysis of increased rosuvastatin absorption by coadministered telmisartan

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- **The Cmax and AUC of rosuvastatin increase when it is coadministered with telmisartan**

- Telmisartan may influence the absorption process of rosuvastatin rather than its metabolic elimination

Park wt al; Transl Clin Pharmacol;2016;24(1):55-62

The Heart Outcomes Prevention Evaluation (HOPE -3) Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf, M.B., B.S., D.Phil., Eva Lonn, M.D., Prem Pais, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Denis Xavier, M.D., Alvaro Avezum, M.D., Ph.D., Lawrence A. Leiter, M.D., Leopoldo S. Piegas, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Karen Sliwa, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Jose L. Accini, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Hyejung Jung, M.Sc., Lisheng Liu, M.D., Rafael Diaz, M.D., Antonio Dans, M.D., and Gilles Dagenais, M.D., for the HOPE-3 Investigators†

Combination therapy (with a statin and anti-hypertensives) would perform best in patients with hypertension, whereas statins alone would perform best in those without elevated blood pressure.

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

The effect of combining rosuvastatin with sartans of different peroxisome proliferator receptor-γ activating capacity on plasma 8-isoprostane prostaglandin F_{2a} levels

Christos V. Rizos[1], Evangelos N. Liberopoulos[1], Constantinos C. Tellis[2], Alexandros D. Tselepis[2], Moses S. Elisaf[1]

- Oxidative stress is associated with the development and progression of cardiovascular disease.
- Plasma 8-isoprostane prostaglandin F2a (8-iso-PGF2a) levels are a reliable marker of oxidative stress
- Patients (*n* = 151) with hypertension, dyslipidemia and impaired fasting glucose were randomly allocated to rosuvastatin (10 mg/day) plus telmisartan 80 mg/day (RT group, *n* = 52) or irbesartan 300 mg/day (RI group, *n* = 48) or olmesartan 20 mg/day (RO group, *n* = 51).

Rizos et al;Arch Med Sci. 2013 Feb 21;9(1):172-6

Results

- A decrease of 8-iso-PGF2a levels vs baseline was observed only in the RT group (–8.6%; $p = 0.02$).

- **Conclusions:**

  The combination of rosuvastatin with sartans of different peroxisome proliferator receptor-γ activating capacity was associated with a decrease in levels of plasma 8-iso-PGF2a.
  - This decrease reached significance only in the telmisartan group

Rizos et al;Arch Med Sci. 2013 Feb 21;9(1):172-6

Atherosclerosis. 2014 Mar;233(1):291-9. doi: 10.1016/j.atherosclerosis.2013.12.004. Epub 2014 Jan 10.

Treatment with telmisartan/rosuvastatin combination has a beneficial synergistic effect on ameliorating Th17/Treg functional imbalance in hypertensive patients with carotid atherosclerosis.

Liu Z[1], Zhao Y[2], Wei F[3], Ye L[4], Lu F[2], Zhang H[2], Diao Y[2], Song H[2], Qi Z[2].

- Th17/Treg cell functional imbalance is correlated to carotid atherosclerosis in hypertensive patients.
- Telmisartan can ameliorate Th17/Treg functional imbalance beyond blood pressure lowering.
- Rosuvastatin can ameliorate Th17/Treg functional imbalance beyond blood lipids lowering.
- Telmisartan/rosuvastatin combination has a beneficial synergistic effect on ameliorating Th17/Treg functional imbalance.

Liu Z et al. Atherosclerosis. 2014 Mar;233(1):291-9

Clin Ther. 2010 Mar;32(3):492-505. doi: 10.1016/j.clinthera.2010.03.018.

Effects of rosuvastatin combined with olmesartan, irbesartan, or telmisartan on indices of glucose metabolism in Greek adults with impaired fasting glucose, hypertension, and mixed hyperlipidemia: a 24-week, randomized, open-label, prospective study.

Rizos CV[1], Milionis HJ, Kostapanos MS, Florentin M, Kostara CE, Elisaf MS, Liberopoulos EN.

- 24-week, randomized, open-label study
- After 12 weeks of dietary intervention, patients were randomly allocated to receive rosuvastatin 10 mg/d plus
  - telmisartan 80 mg/d (RT group),
  - irbesartan 300 mg/d (RI group), or
  - olmesartan 20 mg/d (RO group) for 24 weeks.

Rizos CV et al. Clin Ther. 2010 Mar;32(3):492-505

Results

- At 6 months, the Rosuvastatin + telmisartan group had a 29% decrease in HOMA-IR

	HOMA-IR	HR
Rosuvastatin + telmisartan	29% decrease	2.6 [0.6-6.6] to 1.8 [0.5-5.1]
Rosuvastatin + irbesartan	16% increase	2.5 [0.5-6.2] to 2.9 [0.5-8.1]
Rosuvastatin + olmesartan	14% increase	2.4 [0.5-7.9] to 2.7 [0.5-5.2]

- The improvement in the RT group was statistically significant compared with the RI group ($P < 0.01$) and the RO group ($P < 0.05$).

Rizos CV et al. Clin Ther. 2010 Mar;32(3):492-505

Summary

- Dyslipidemia and hypertension are the established risk factors of prime importance in cardiovascular diseases
- The risk of CVD associated with concomitant hypertension and dyslipidemia is more multiplicative than the sum of the individual risk factors
- Many patients treated with currently available antihypertensive and statin monotherapies do not achieve desired goals
- The fixed dose combination can provide better BP control and lipid targets and thereby better cardiovascular protection

Thank You