ROVATITAN®
Rosuvastatin / Valsartan

An Effective Combination Therapy for Hypertension & Dyslipidemia

Focused on ROVATITAN Study

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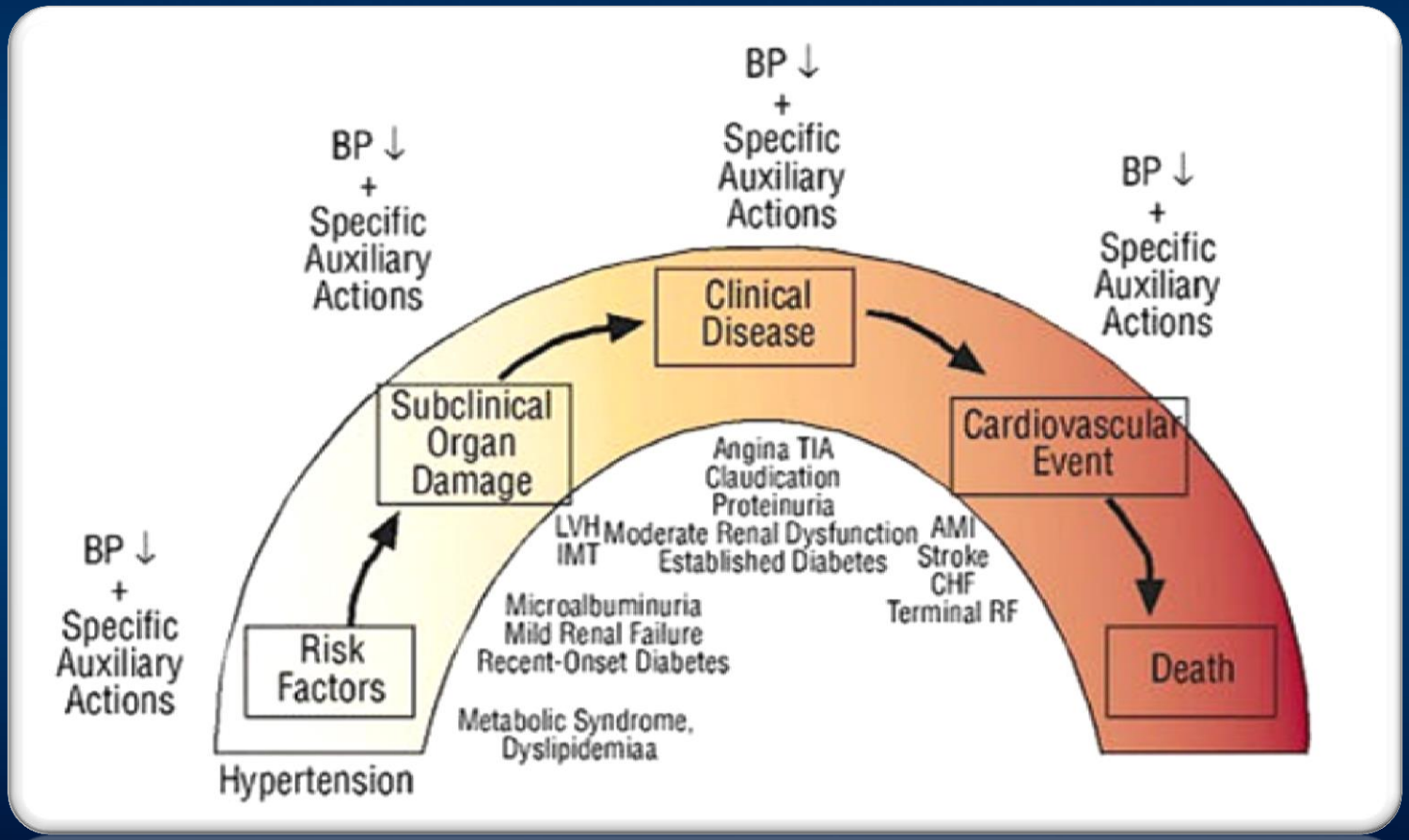
Introduction

Cardiovascular Disease Continuum

Aggressive management can identify patients at early CVD risk and slow or halt the progression of disease at all points along the CVD continuum



Circulation 2006;114(25):2850-70.

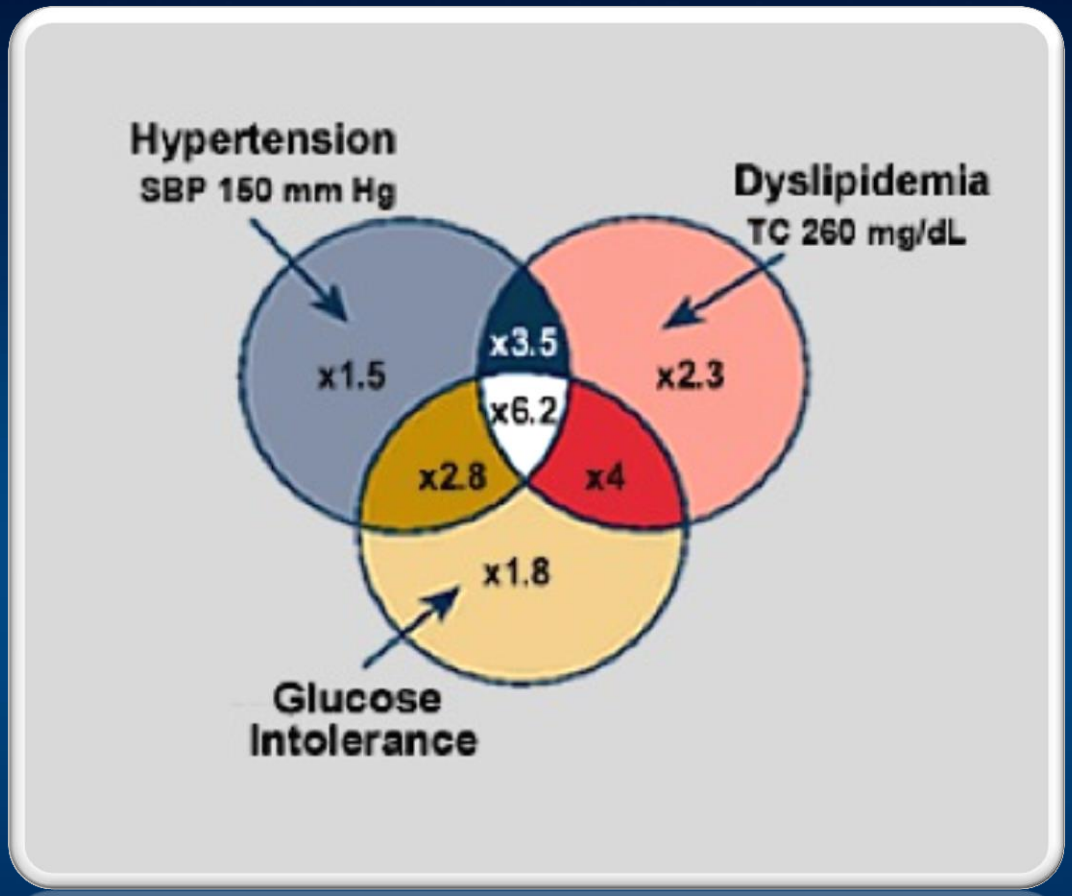
Coprevalence of 'Modifiable' CV Risk Factors

	Percent Chance of Also Having					
Primary Diagnosis	Hypertension	Dyslipidemia	Diabetes	Hypertension/ dyslipidemia	Hypertension/ diabetes	Dyslipidemia/ diabetes
Hypertension		62	16			13
Dyslipidemia	44		15		10	
Diabetes	64	85		54		
Hypertension/ dyslipidemia			22			
Hypertension/ diabetes		84				
Dyslipidemia/ diabetes	64					

Cardiovascular risk factors tend to cluster.

Data on file, Pfizer Inc, New York, NY

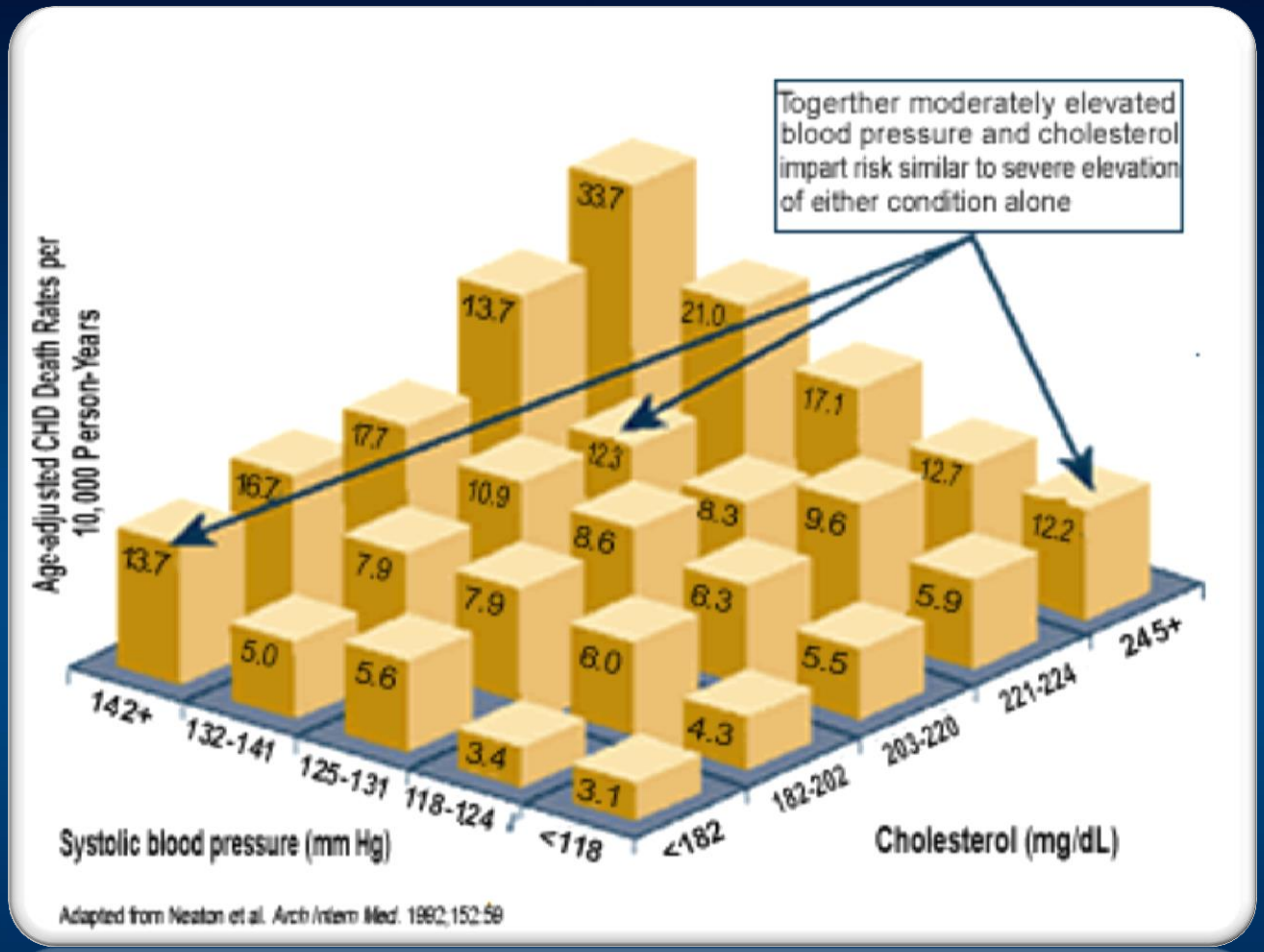
Impact of Multiple CV Risk Factors on Individual CV Risk



Multiple risk factors have a multiplicative impact.

Addapted from Kannel WB. Hypertension:Physiopathology and Treatment.1997

Multiple Risk Factor Intervention Trial (MRFIT)

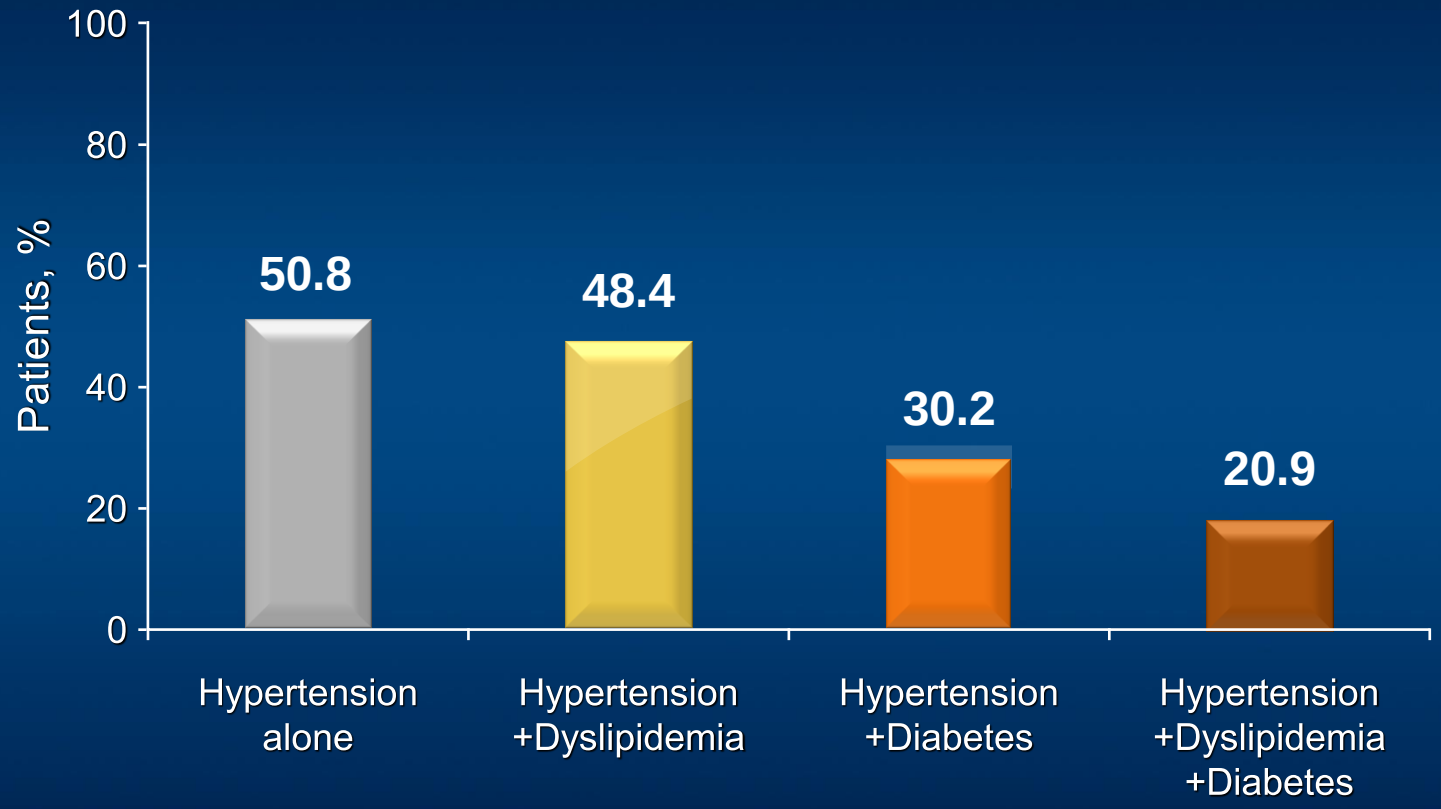


Even mild-to-moderate levels of multiple risk factors impart substantial risk.

Neaton JD, Wentworth D,. Arch Intern Med.1992;152:56-64

Many patients are not reaching treatment goals

Percentage of Patients Achieving Blood Pressure Goal



Target BP < 140/90 mmHg (for diabetes < 130/85 mmHg)

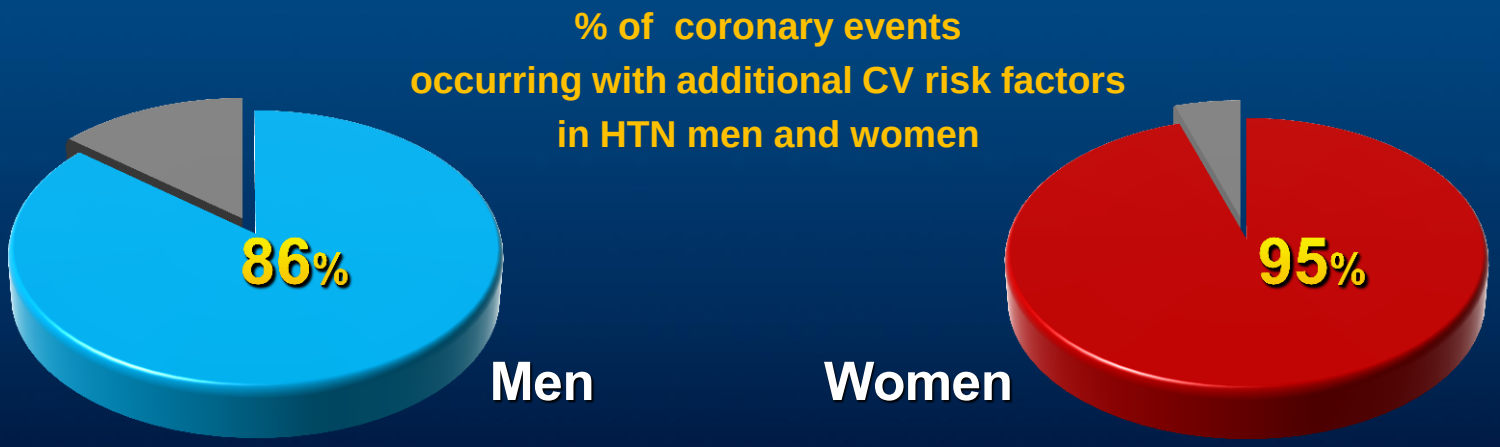
Poster(1203-132) presented at: American College of Cardiology, 52nd Annual Scientific Session; 2003

Needs of Simultaneous Targeting

An optimal treatment plan for patients with hypertension involves simultaneously targeting both blood pressure and atherosclerosis.

Distinct outcomes between different treatment regimens suggest that control of BP per se is not the only important consideration.

It is more likely that blood pressure control combined with amelioration of atherosclerosis is essential for preventing and treating CVD.



Atherosclerosis 2010;209(2): 307-313

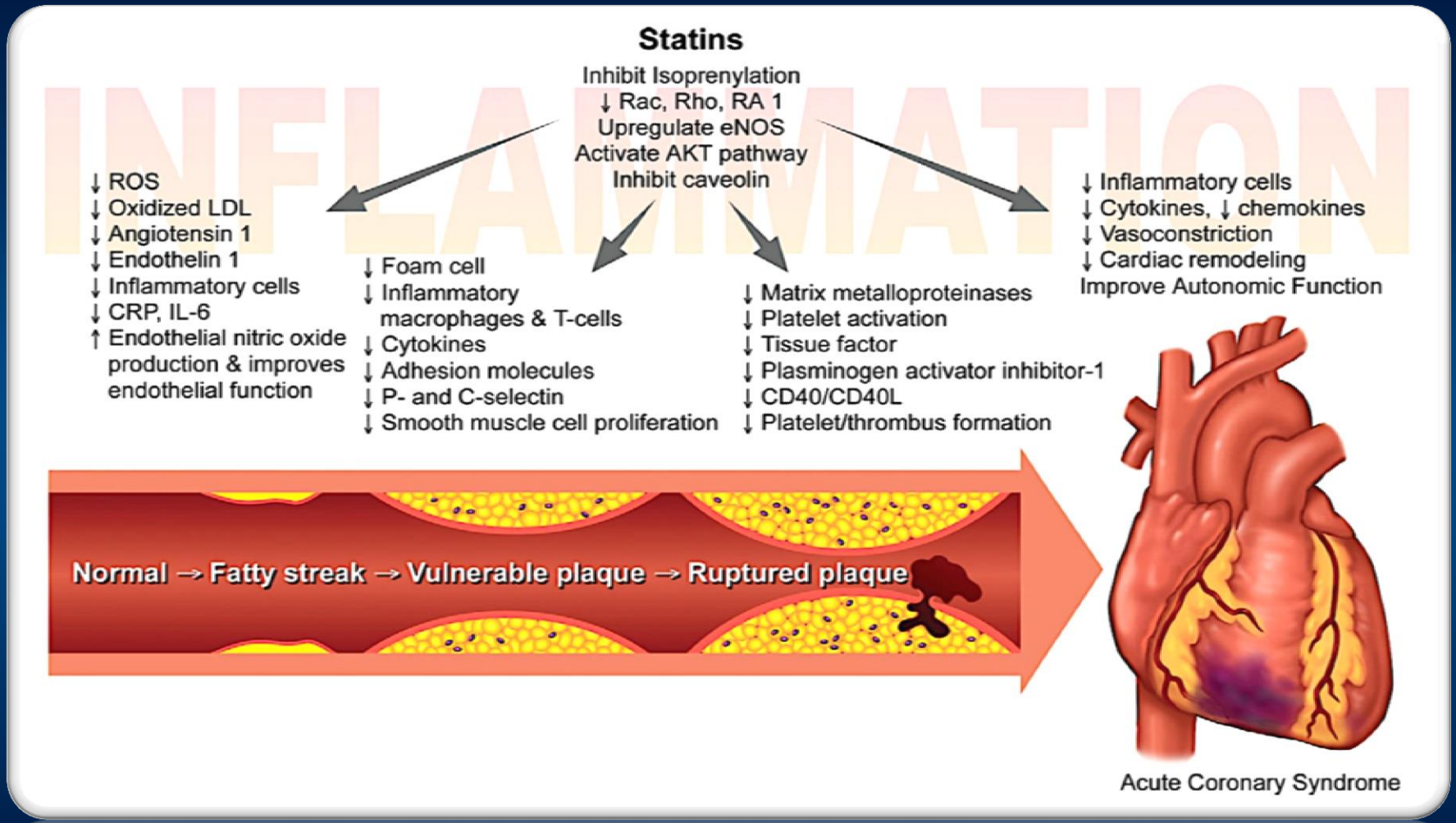
Effect of Lipid-Lowering Treatment on Blood Pressure

Lipid-lowering treatment with statins may have BP–lowering effect.

Source	Study Outline	Drug Used	Final Outcome
O'Callaghan et al, 1994	25 Patients with hypertension and hyperlipidemia.	Pravastatin sodium vs placebo for 12 wk	Pravastatin did not lower blood pressure
Abetel et al, 1998	23 Patients with hypertension and hyperlipidemia.	Fluvastatin sodium, 40 mg, for 3 mo	Fluvastatin lowered blood pressure by 8-16 mm Hg
Glorioso et al, 2000	25 Patients with hypertension and hyperlipidemia	Pravastatin sodium, 20-40 mg vs placebo for 32 wk	Pravastatin decreased SBP by 8 mm Hg
Sposito et al, 1999	Patients with hypertension and hyperlipidemia	ACE inhibitor (enalapril maleate or lisinopril) alone or with statin (lovastatin or pravastatin)	Additive blood pressure-lowering effect of the combination compared with ACE inhibitor alone
Borghi et al, 2000	Patients with hypertension and hyperlipidemia	Statins (pravastatin or simvastatin) in addition to antihypertensive treatment	Additive benefit of statins in blood pressure lowering shown
Tonolo et al, 2000	26 Microalbuminuric hypertensive patients with type 2 diabetes mellitus	Simvastatin in addition to antihypertensive treatment	Simvastatin exerted additional blood pressure-lowering effect and also reduced 24-h urinary albumin excretion
Jonkers et al, 2001	17 Patients with hypertriglyceridemia and hypertension.	Bezafibrate	Bezafibrate reduced SBP by 5 mm Hg

Arch Intern Med 2003;163(11):1296-1304

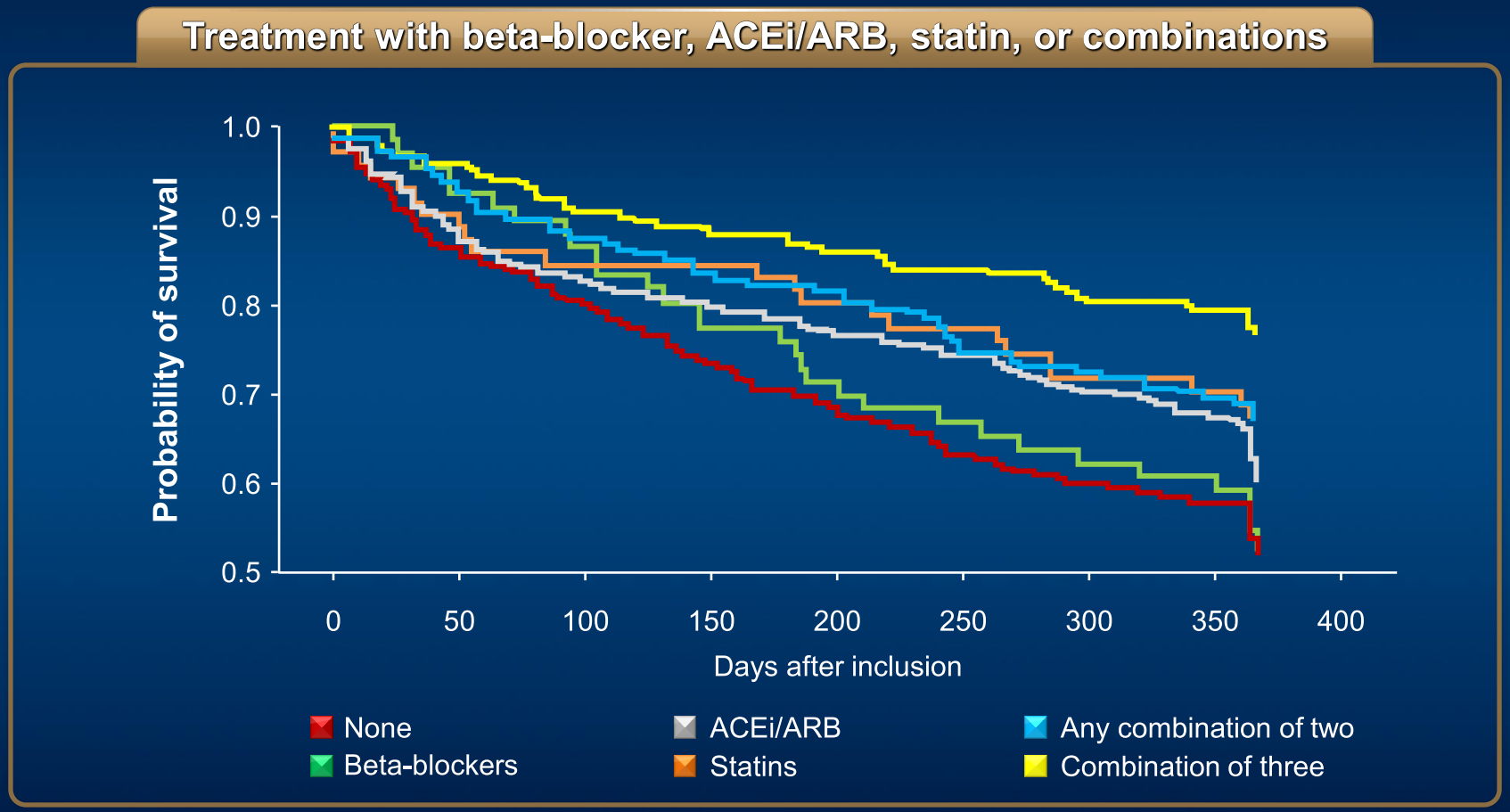
Pleiotropic Effects of Statin



Adapted from Patel TN, et al., Eur Heart J 2007;28:664-72

Benefit of Combination Therapy

Combination therapy was associated with longer survival times.



Kaplan–Meier curves detailing survival time after inclusion in a multicentre cohort of Spanish polypathological patients depending on the chronic prescription of ACEi/ARB, beta-blockers, and statins, alone or in combination.

Eur J Intern Med 2012;23(2):179-84

Factors to consider in choosing specific molecule

ARB	Statin
✓ **Blood pressure lowering effect** ✓ **Proven by large-scale clinical evidence** ✓ **Prevention of comorbidities in patients with hypertension or heart failure** ✓ **Special patient population consideration** (ex. diabetes, HF) ✓ **Additional consideration** • Compliance & persistence • Cost-effectiveness	✓ **Lipid lowering potency** ✓ **Stage of natural history of metabolic and cardiovascular disease** ✓ **Phenotype** : age, sex, smoking, obesity, diabetes, and previous statin use and other concomitant drug use ✓ **Additional consideration** • Bioavailability (drug-drug interaction) • Lipophilicity • Pleiotropic effect ✓ **Side effects**

Int J Cardiol 2013;167(5):1696-702

Valsartan has been a 'Able' ARB

ARB

- ✓ Blood pressure lowering effect
- ✓ Proven by large-scale clinical evidence
- ✓ Prevention of comorbidities in patients with hypertension or heart failure
- ✓ Special patient population consideration (ex. diabetes, HF)
- ✓ Additional consideration
  - Compliance & persistence
  - Cost-effectiveness

Valsartan

- Powerful blood pressure reduction
- The variety of clinical evidences related to CHD (HF, LVH)
- The only ARB approved for indication proving increase in survival rate in post MI patients
- The renal protection effect (reducing albuminuria)

Rosuvastatin has been Powerful

Statin

- ✓ Lipid lowering potency
- ✓ Stage of natural history of metabolic and cardiovascular disease
- ✓ **Phenotype**
  : age, sex, smoking, obesity, diabetes, and previous statin use and other concomitant drug use
- ✓ **Additional consideration**
  - Bioavailability (drug-drug interaction)
  - Lipophilicity
  - Pleiotropic effect
- ✓ Side effects

Rosuvastatin

- **Significantly effective in reducing LDL level, increasing HDL level**
- **The first statin to proved in being effective to retard development of atherosclerosis**
- **Indication for reducing CVD risk (JUPITER study)**
- **Low Drug-Drug interaction**

Objective of project

Valsartan-Rosuvastain Program - Objective

Efficacy

- BP & LDL-C reduction equivalent to or better than mono therapy

Safety

- Feel free to any other SE
- Broad safety margin

Compliance

- Dose flexibility with a variety of strength
- No drug-drug interaction profiles

Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K.

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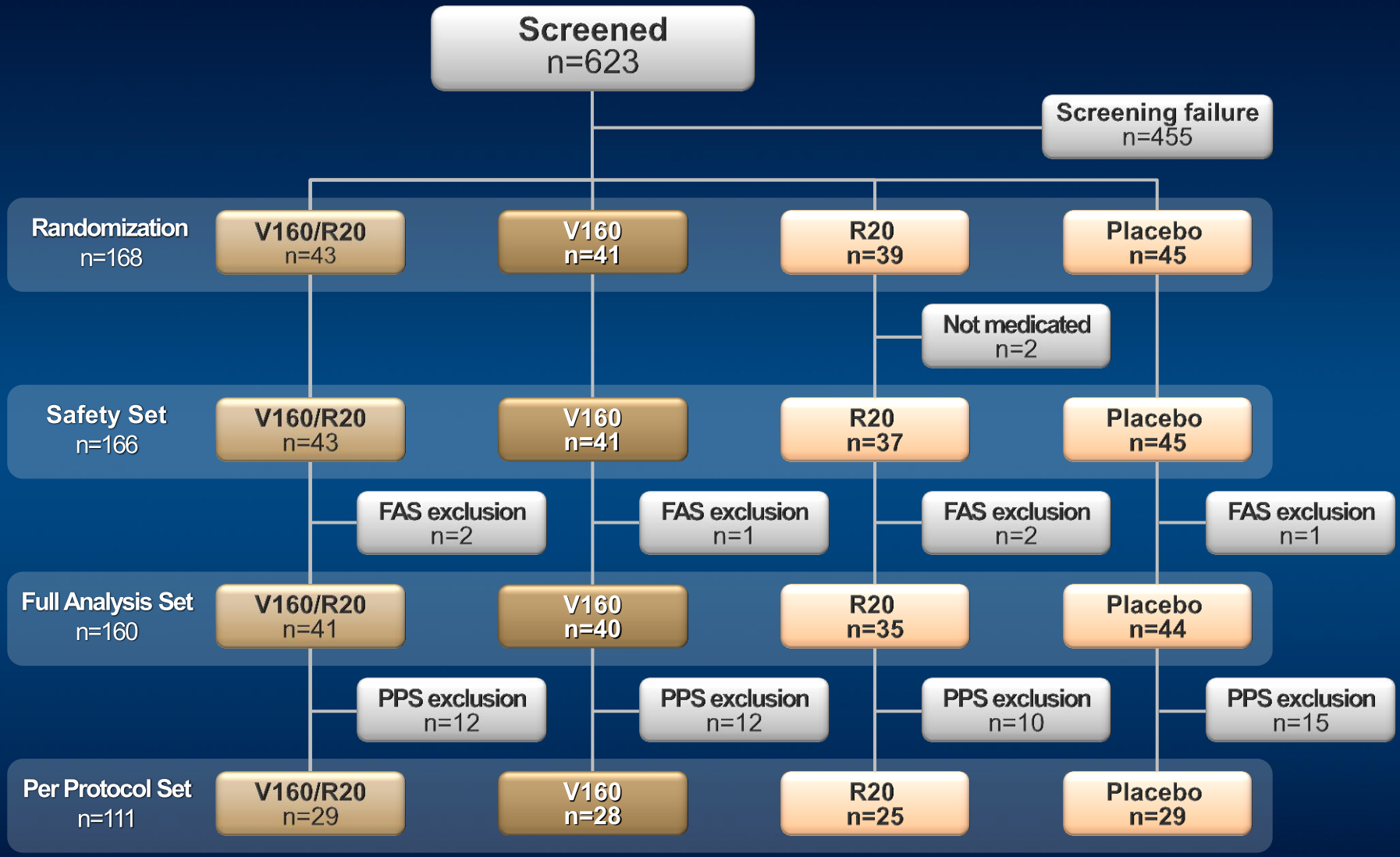
Overview of design of phase III clinical trials

Phase III Study Design

- 8-week, multicenter, randomized, double-blind phase III clinical study
- Evaluate the efficacy and safety of Valsartan 160mg+Rosuvastatin 20mg, Valsartan 160mg, Rosuvastatin 20mg vs. plcebo in patients with essential hypertension and hyperlipidemia.
- **Primary endpoint :**
  1) Mean change in sitDBP at 8 weeks with Valsartan 160mg+Rosuvastatin 20mg and Rosuvastatin alone
  2) Percent change in LDL-C at 8 weeks with Valsartan 160mg+Rosuvastatin 20mg and Valsartan alone

*TLC (Therapeutic Lifestyle Change)

Subject Disposition



Subject Demography

No statistically significant differences

	V160/R20	V160	R20	Placebo
	(n=41)	(n=40)	(n=35)	(n=44)
Age (yrs)	61.05	62.65	60.74	60.98
Gender				
Male (%)	25 (60.98)	26 (65.00)	28 (80.00)	34 (77.27)
Female (%)	16 (39.02)	14 (35.00)	7 (20.00)	10 (22.73)
Weight (kg)	67.6	67.82	71.62	70.12
Height (cm)	163.79	163.47	167.18	166.89
BMI (kg/m^2)	25.09	25.31	25.54	25.1
HTN diagnosed at screening (%)				
Yes (%)	6 (14.63)	2 (5.00)	5 (14.29)	3 (6.82)
No (%)	35 (85.37)	38 (95.00)	30 (85.71)	41 (93.18)
Duration of Hypertension (yrs)	6.94	7.5	6.81	4.78
Hyperlipidemia diagnosed at screening (%)				
Yes (%)	7 (17.07)	8 (20.00)	8 (22.86)	7 (15.91)
No (%)	34 (82.93)	32 (80.00)	27 (77.14)	37 (84.09)
Duration of Hyperlipidemia (yrs)	4.76	4.31	3.84	3.22

Data on File LG-VRCL 002, LG Life Sciences.

Baseline blood pressure & LDL-C information

No statistically significant differences

	V160/R20	V160	R20	Placebo
	(n=41)	(n=40)	(n=35)	(n=44)
sitSBP(mmHg)	146.27	152.83	150.33	147.50
sitDBP(mmHg)	93.71	92.80	93.71	93.35
LDL-C(mg/dL)	158.39	154.63	145.43	154.39
TC(mg/dL)	242.56	230.45	223.37	236.48
TG(mg/dL)	185.17	152.23	158.91	177.50
HDL-C(mg/dL)	48.39	49.37	49.93	48.56
Apo A1(mg/dL)	139.07	137.65	139.20	138.55
Apo B(mg/dL)	144.66	137.80	131.74	143.86

Data on File LG-VRCL 002, LG Life Sciences.

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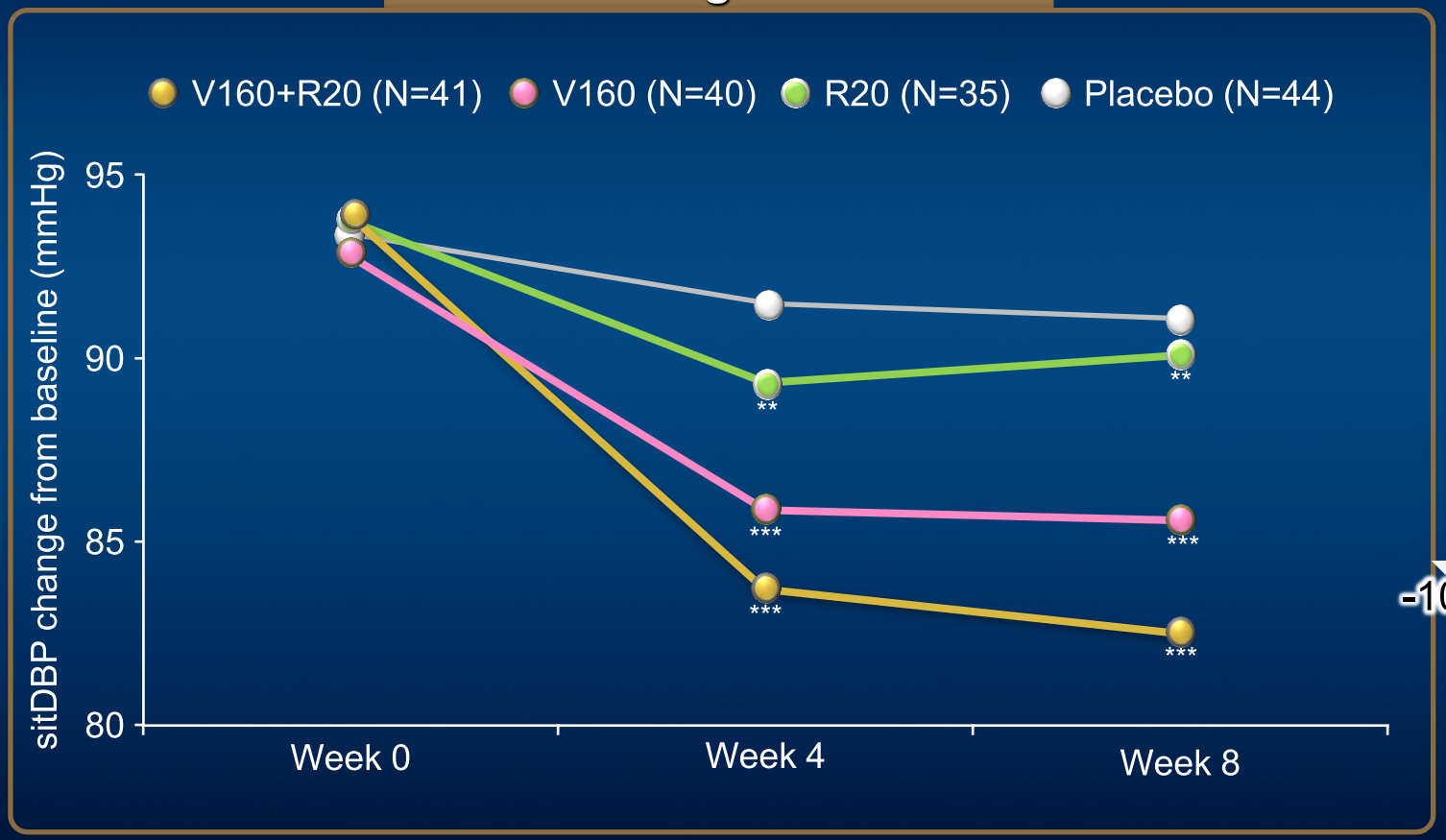
Synergic effect on BP reduction compared to valsartan alone

Synergistic effect on Reduction in Blood Pressure

Additional BP lowering effects of Rovatitan compared to valsartan alone as early as Week 4

Mean change in sitDBP



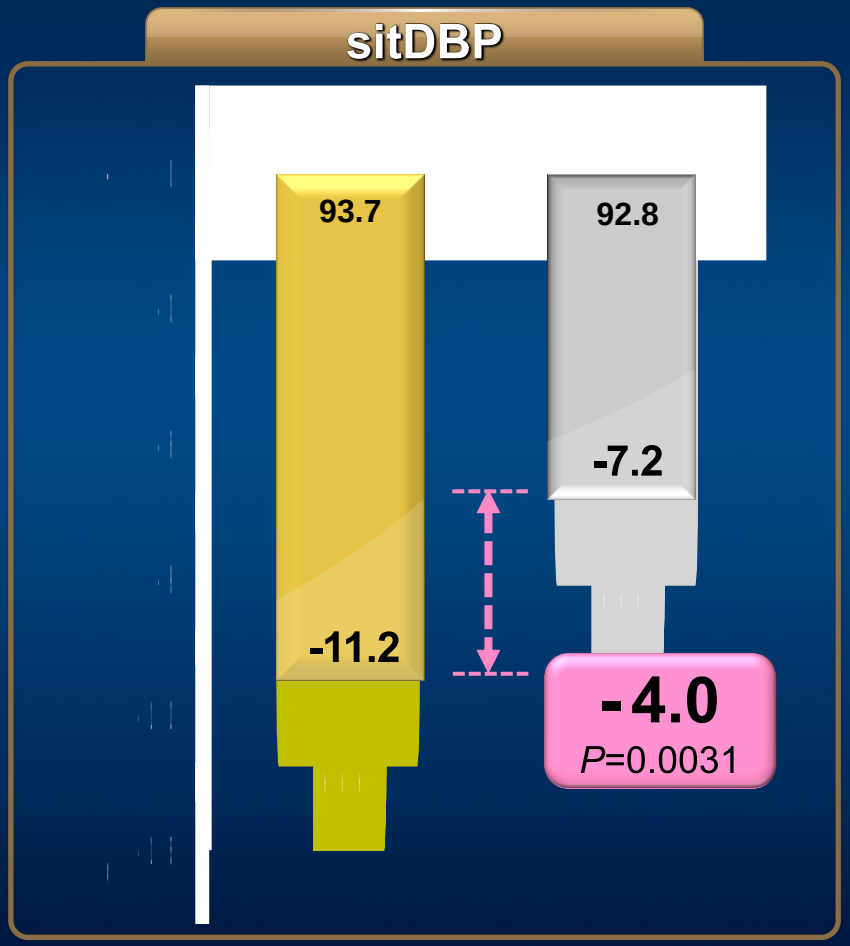
Rovatitan Fast Acting

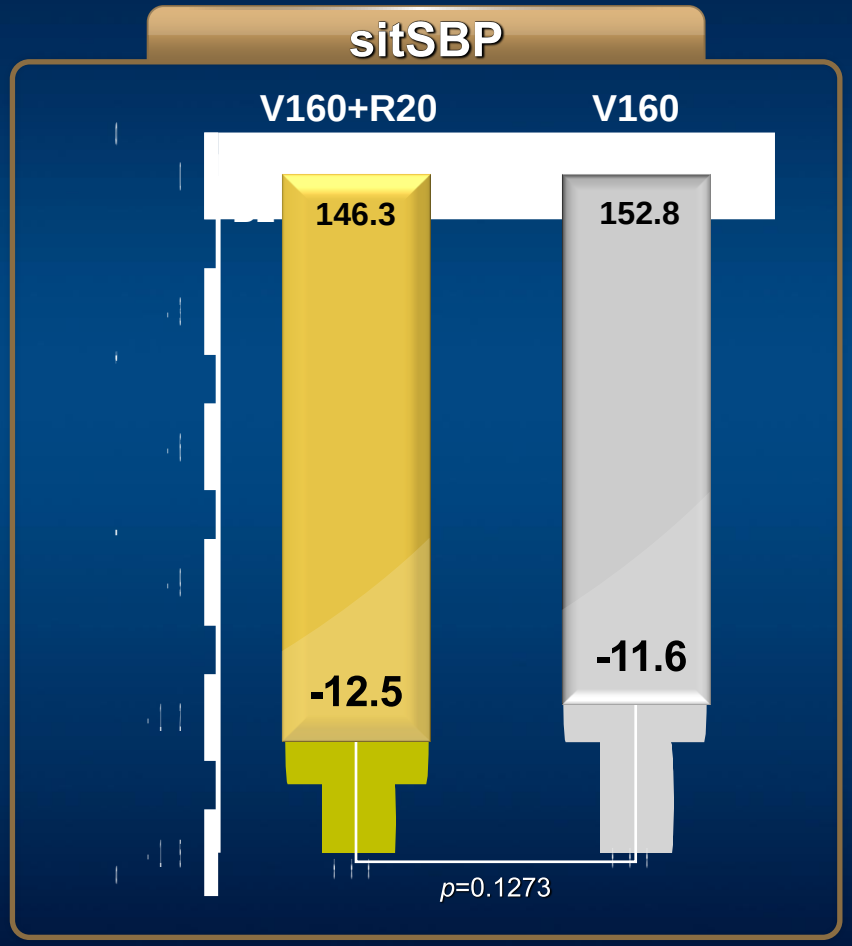
** $p<0.001$ vs. baseline; *** $p<0.0001$ vs. baseline;

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Synergistic effect on Reduction in Blood Pressure

Additional BP lowering effects of Rovatitan compared to valsartan alone at Week 8

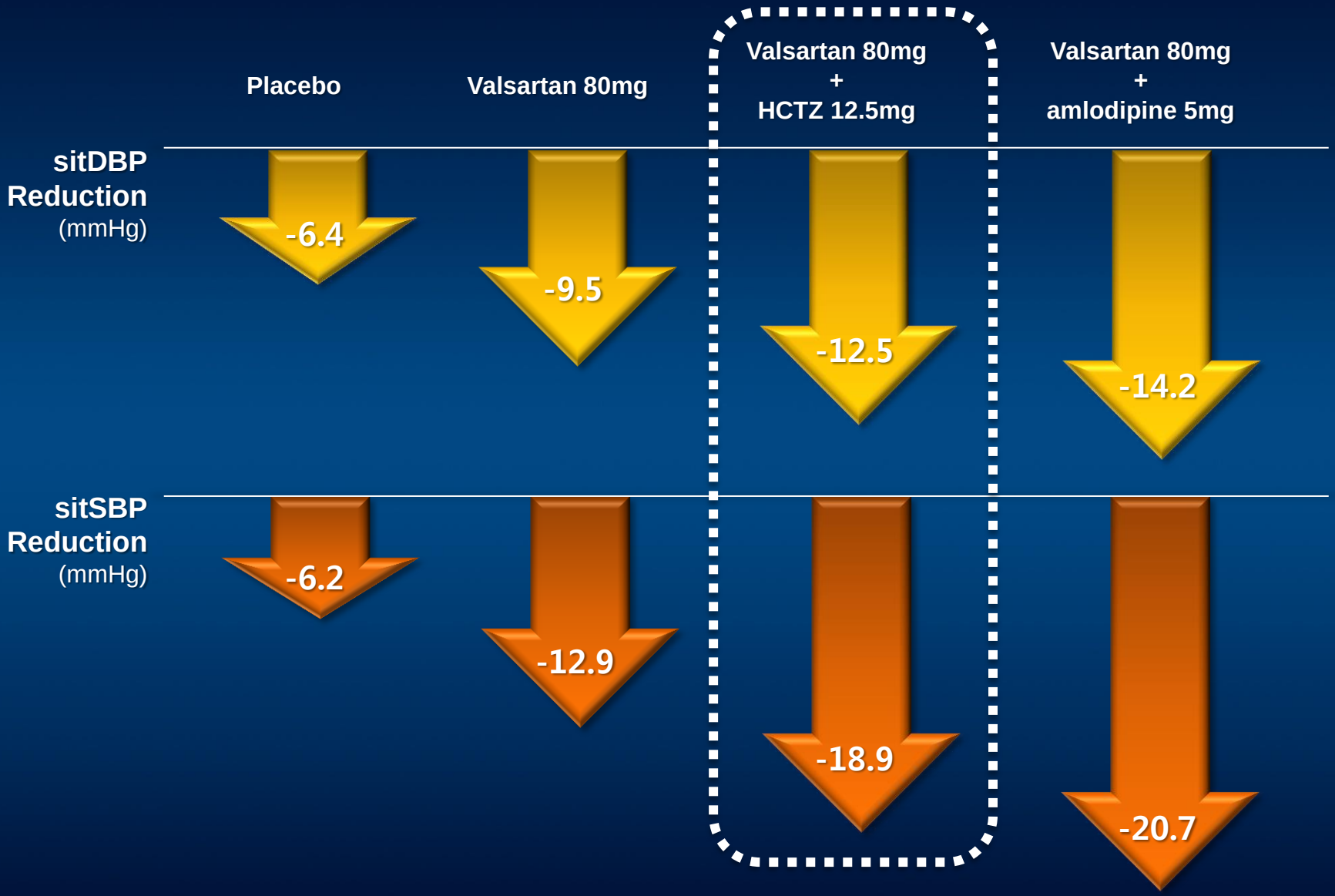




*** $p<0.0001$ vs. baseline;

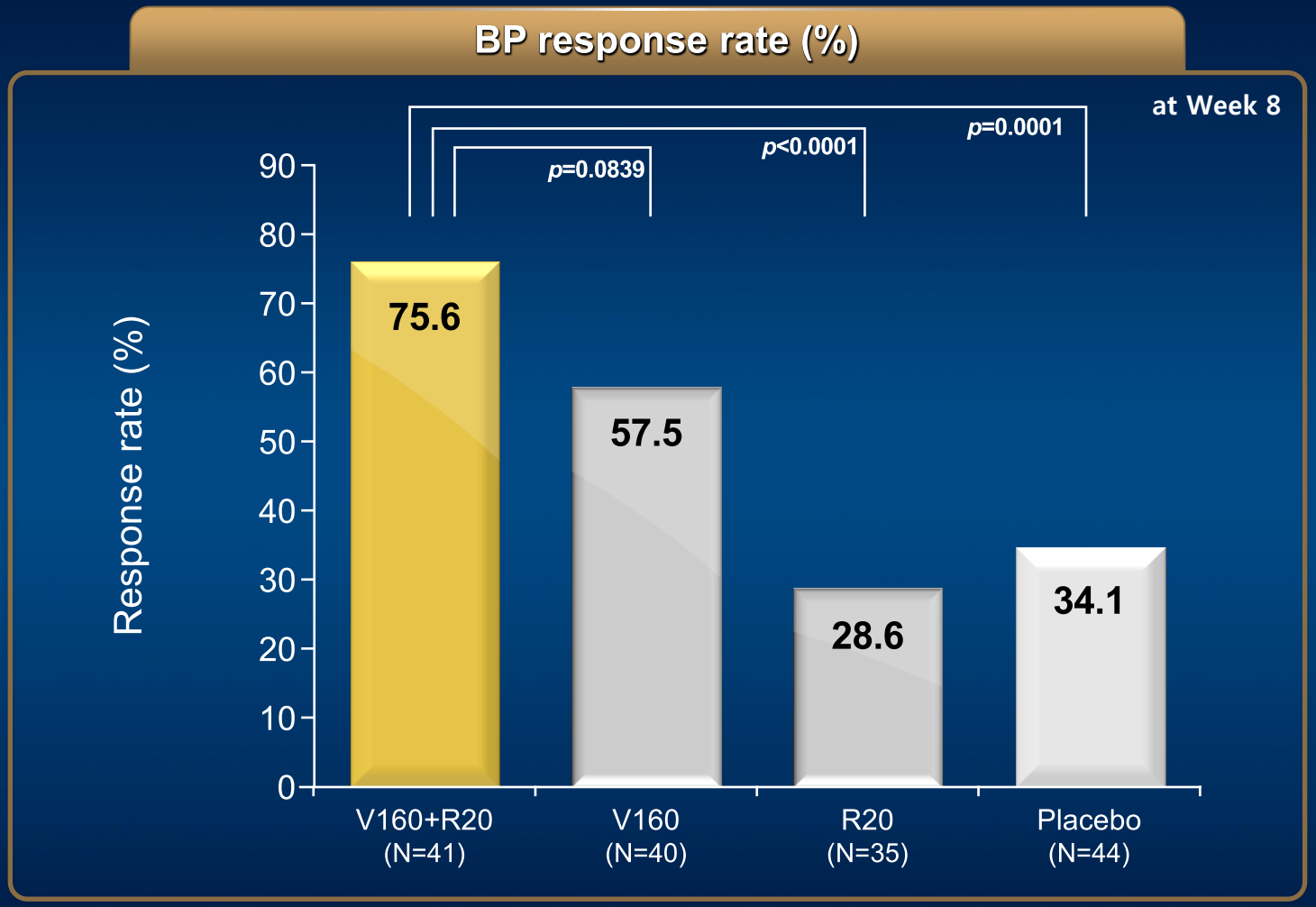
FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Valsartan based BP reduction effect



FDA Label Information

Rovatitan achieved higher BP response rate



BP response rate: sitDBP < 90mmHg or Reduction of sitDBP 10mmHg form baseline
(for high risk group, sitDBP < 80mmHg)

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

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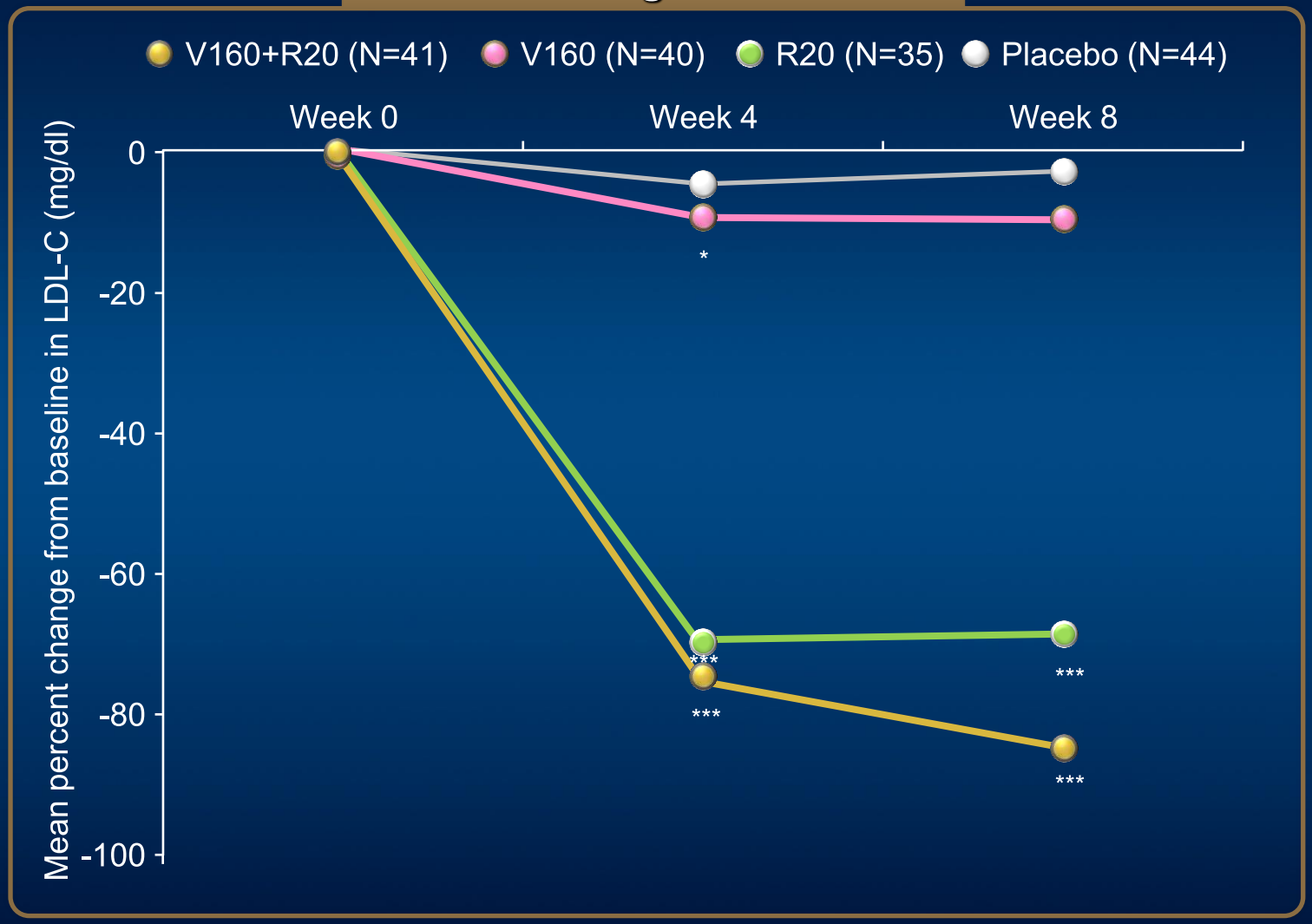
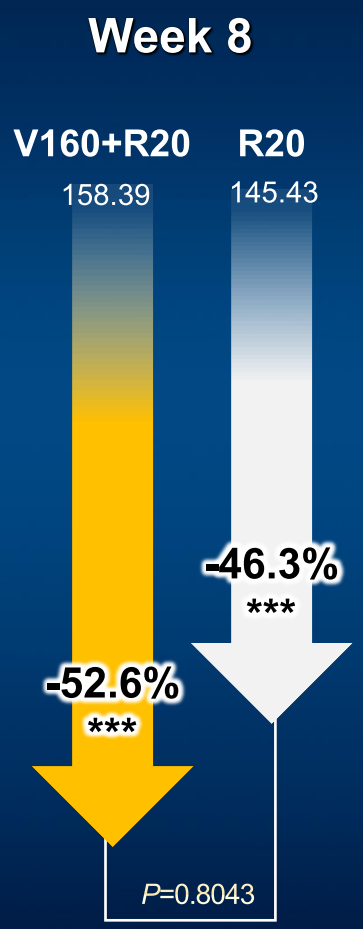
Powerful LDL lowering effect with high intensity statin therapy

Powerful Reduction of LDL-C

Mean change in LDL-C

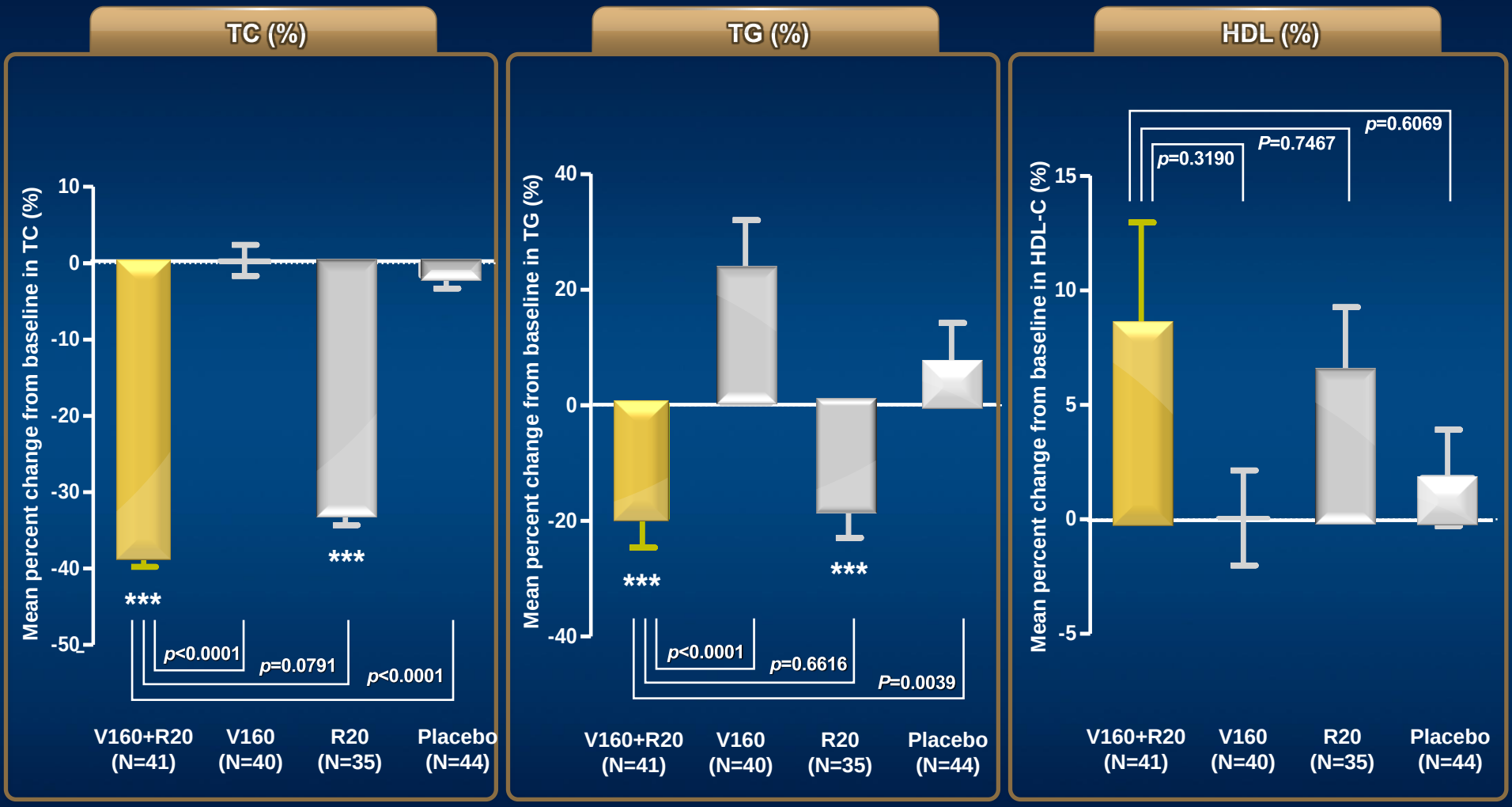




* $p<0.05$ vs. baseline; *** $p<0.0001$ vs. baseline;

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

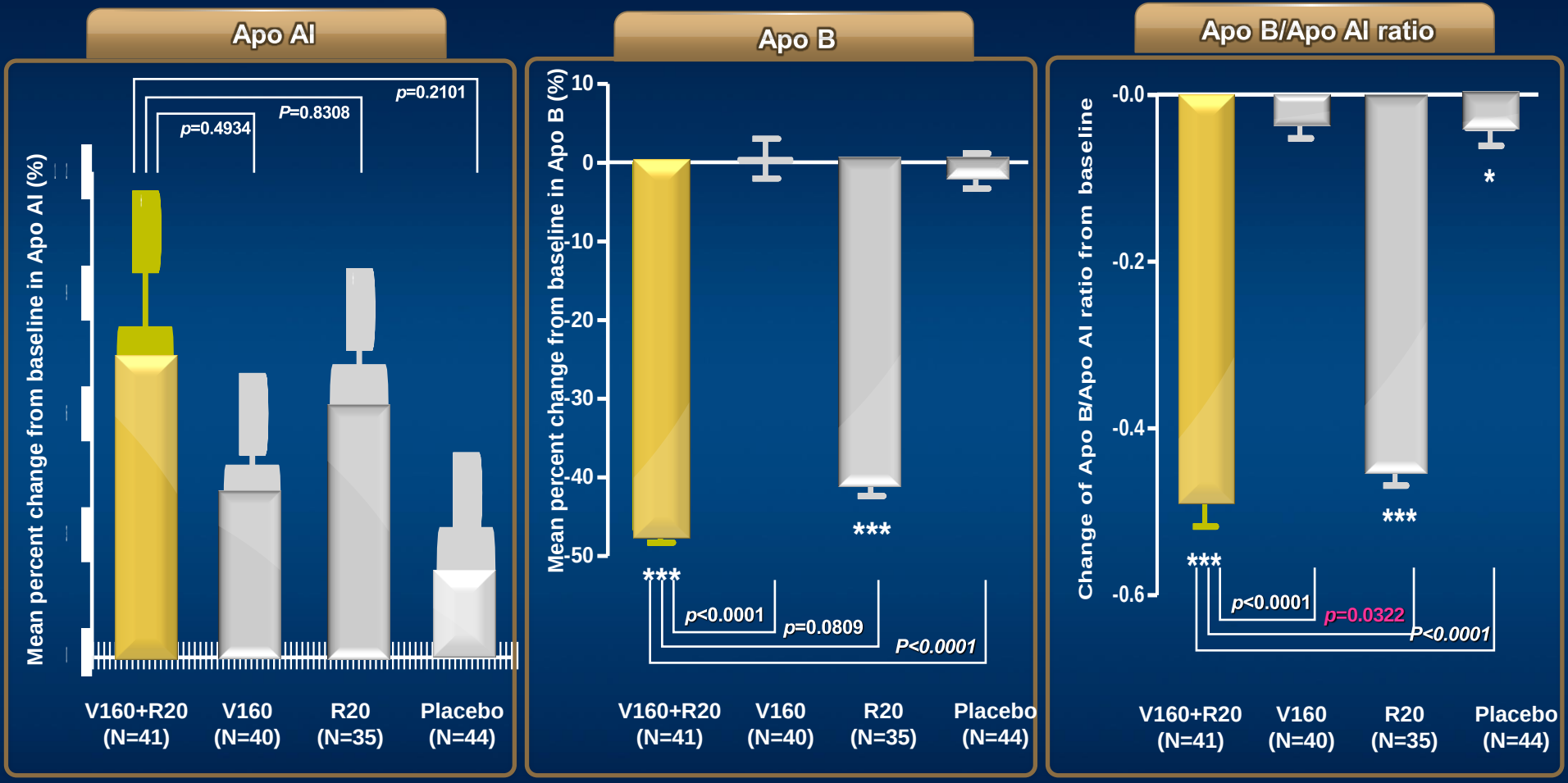
Favorable changes in lipid profile at week 8



*** p<.0001 vs. baseline

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Favorable changes in lipid profile at week 8



** p<0.05 vs. baseline *** p<.0001 vs. baseline*

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

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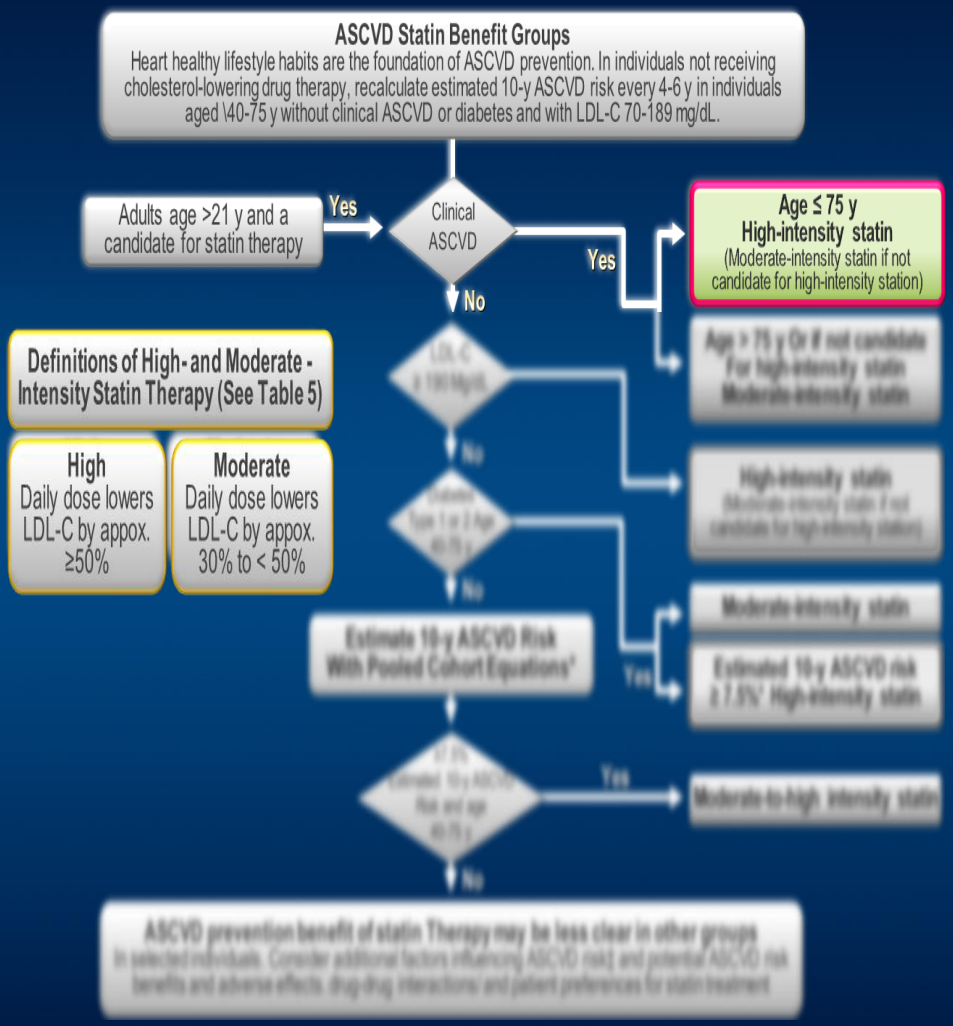
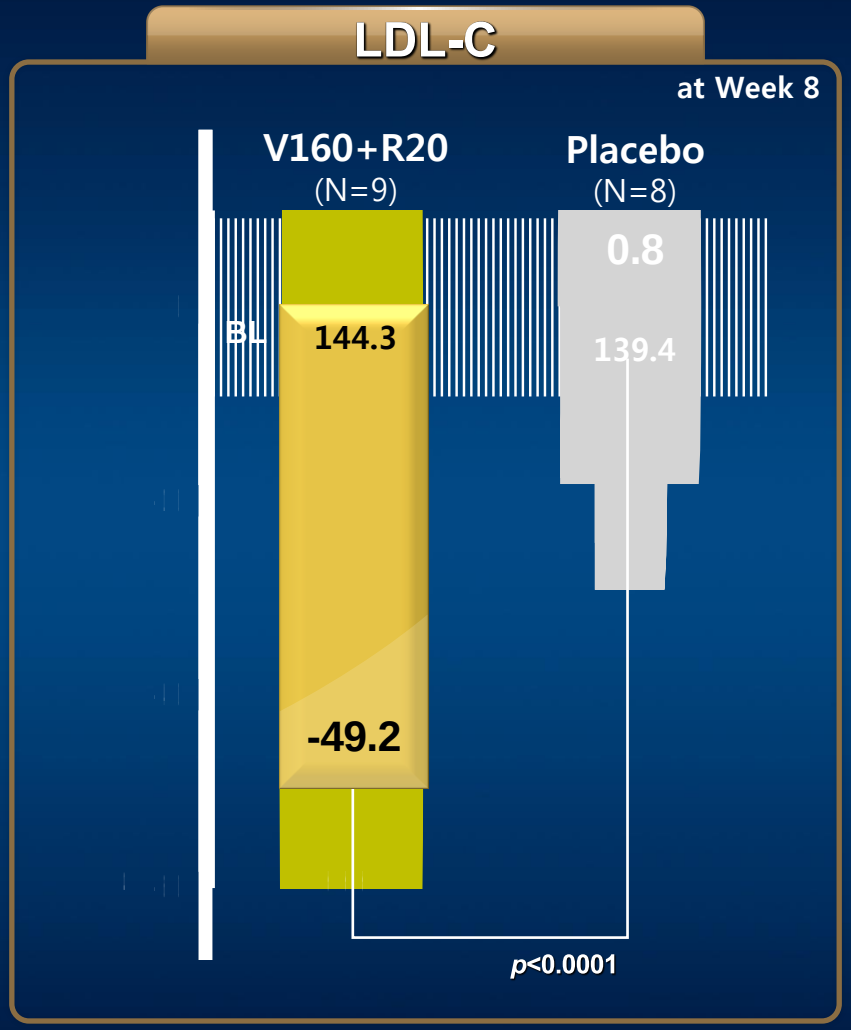
Subgroup analysis

Efficacy in Individuals with known ASCVD

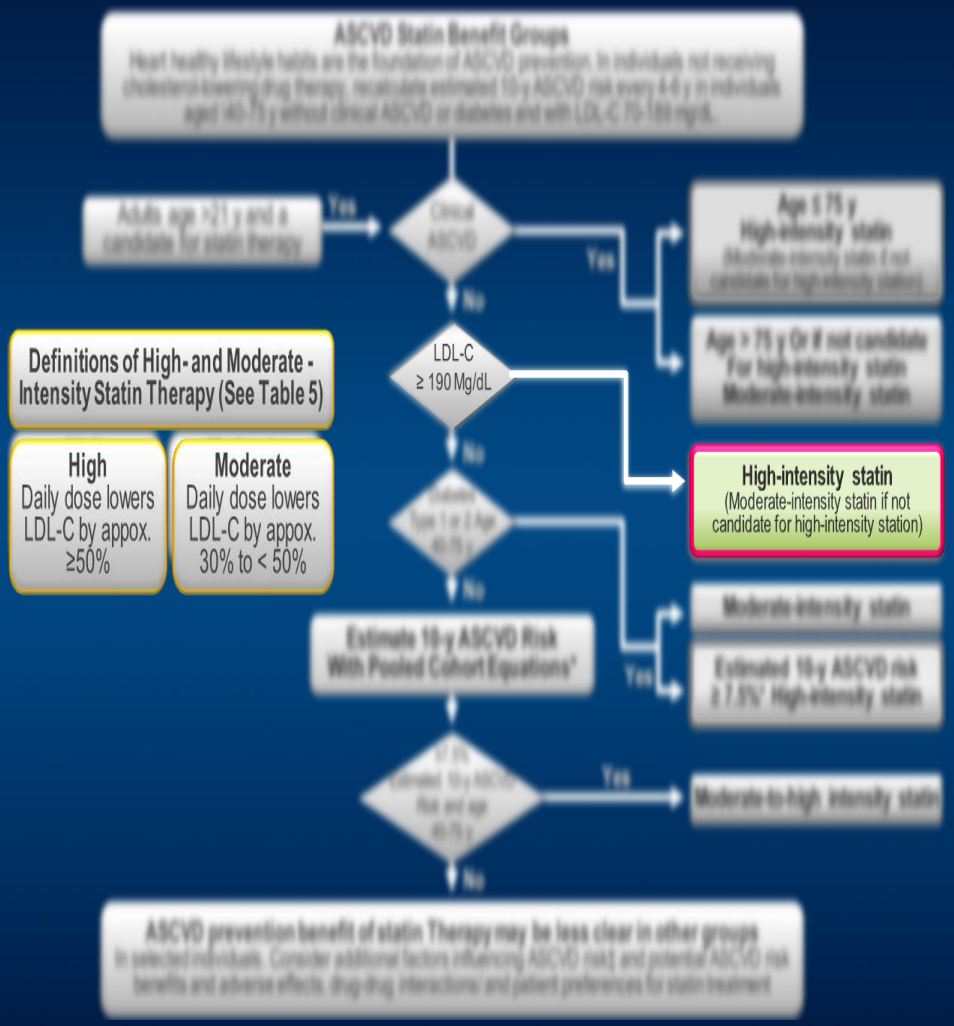


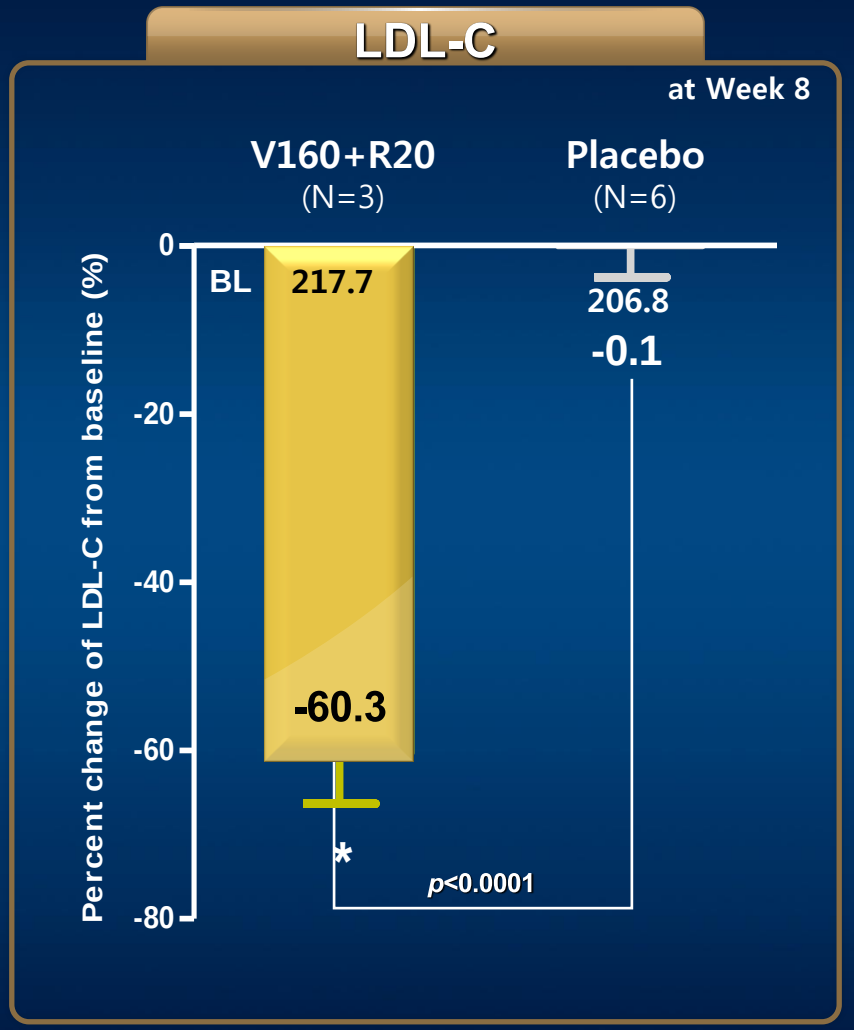


*** $p<0.0001$ vs. baseline

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Efficacy in Individuals with LDL-C≥190 mg/dL

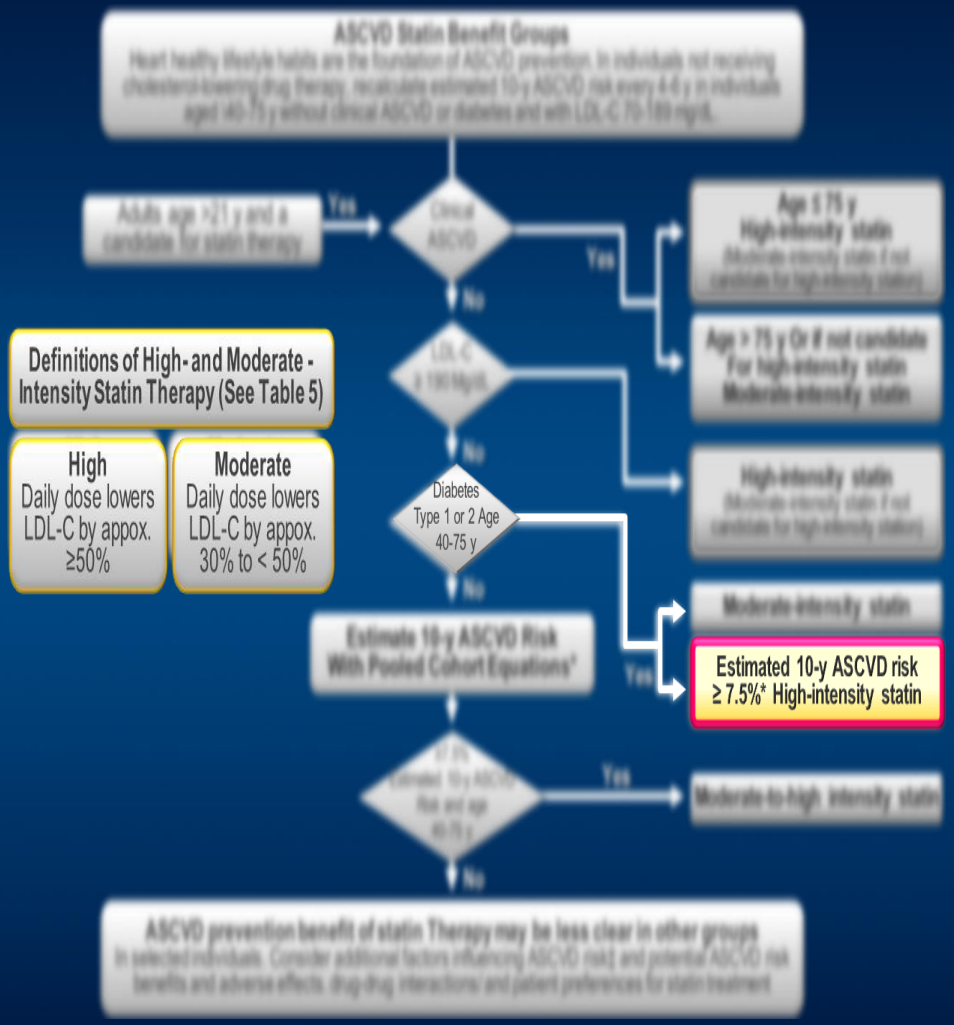


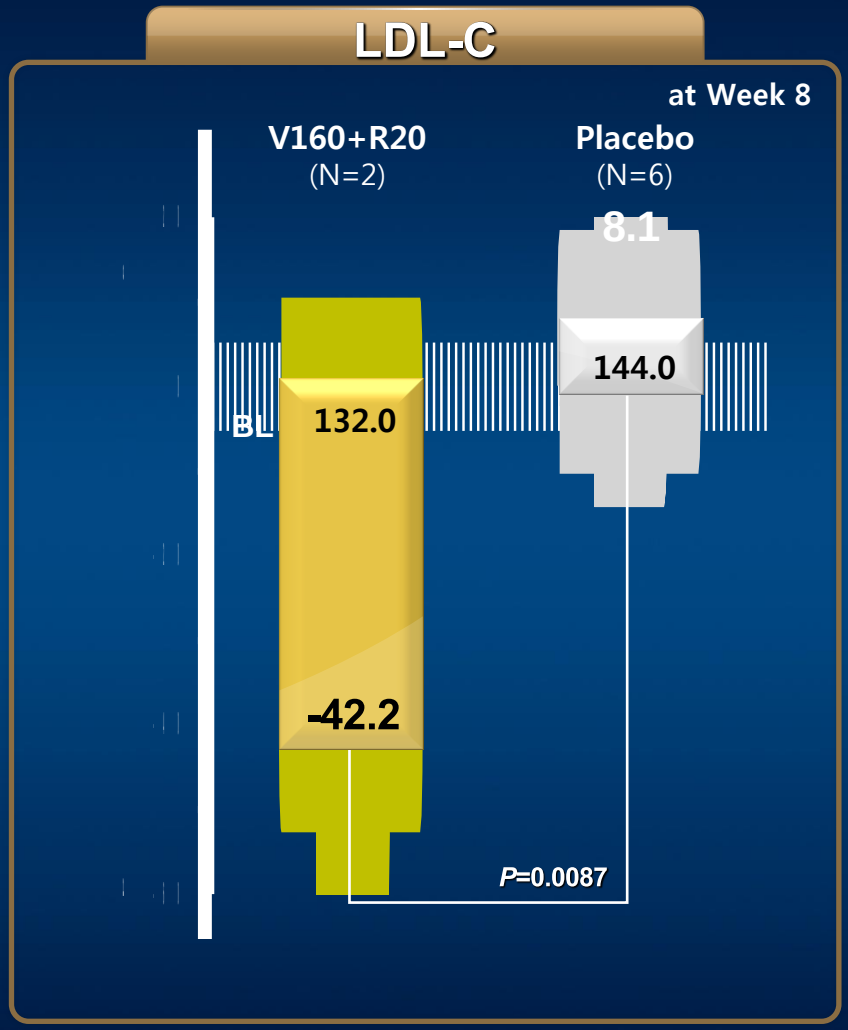


*p<0.01 vs. baseline

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Efficacy in Individuals 40 to 75 years of age with diabetes and LDL-C 70 - 189 mg/dL

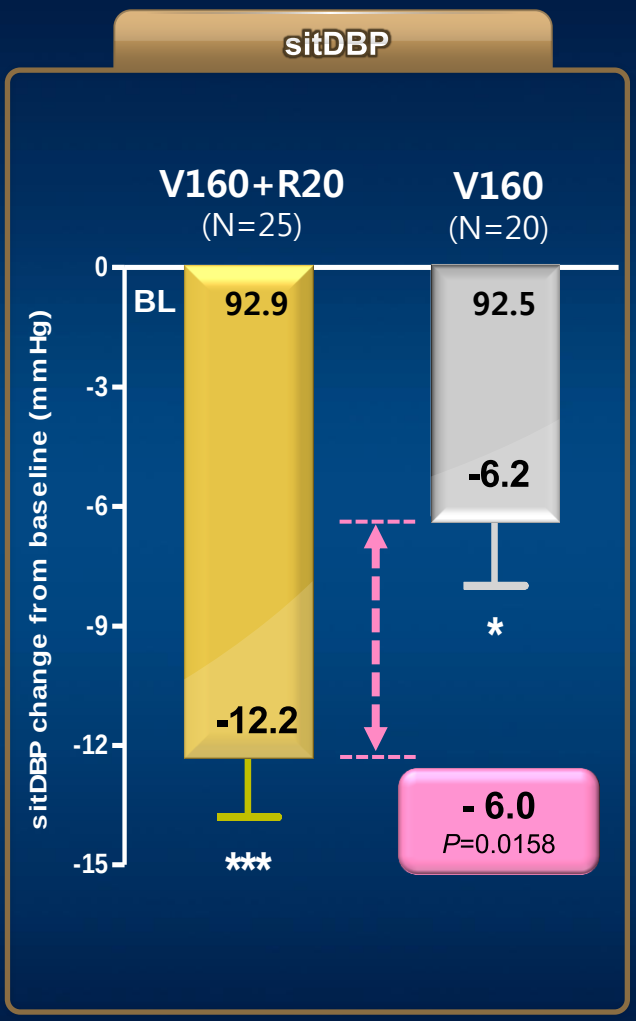


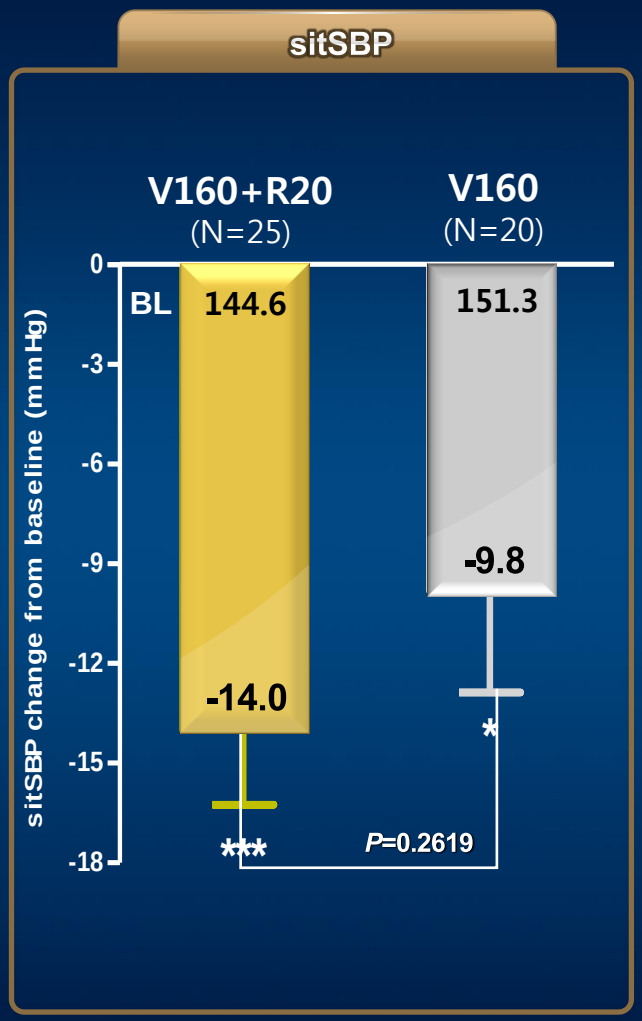


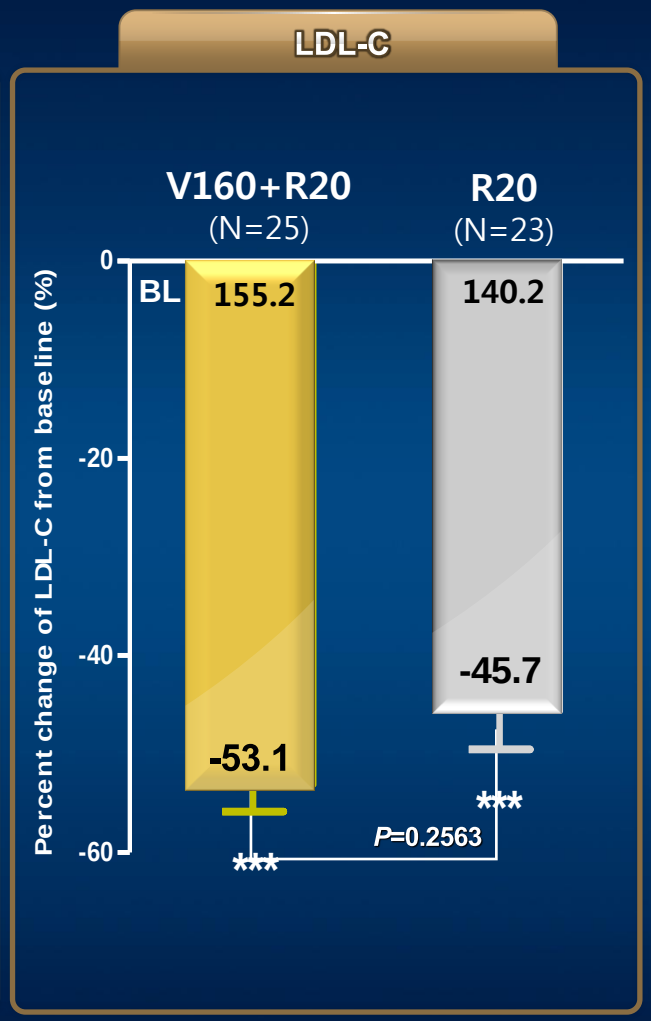
FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Efficacy in Individuals with FPG ≥100mg/dL or diabetes

at Week 8







*** $p<0.0001$ vs. baseline
* $p<0.01$ vs. baseline

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Safety profile

Safety Profile: Summary of Adverse Events

Adverse Events Summary	V160/R20	V160	R20	Placebo
Number of patients	43	41	37	45
Number of patients experienced an AE	10 (23.3%)	7 (17.1%)	4 (10.8%)	5 (11.1%)
Mild	10 (23.3%)	7 (17.1%)	4 (10.8%)	5 (11.1%)
Moderate	1 (2.3%)	1 (2.4%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of patients experienced a SAE	1 (2.3%)	0 (0%)	0 (0%)	0 (0%)
Number of AEs	15	11	7	8
Number of SAEs	1 (6.7%)	0 (0%)	0 (0%)	0 (0%)

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Safety Profile: Summary of Adverse Drug Reactions

Adverse Drug Reactions n (%)	V160/R20 n=43	V160 n=41	R20 n=37	Placebo n=45
Number of patients experienced a ADR	1 (2.3%)	2 (4.9%)	1 (2.7%)	1(2.2%)
Nausea	1 (2.3%)	-	-	-
Chest discomfort	-	2 (4.9%)	-	-
Chest pain	-	-	1 (2.7%)	-
Headache	-	-	-	1 (2.2%)
Hypoaesthesia	-	-	1 (2.7%)	-

FAS Data (Full Analysis Set) Data on File LG-VRCL 002, LG Life Sciences.

Conclusions

- ARB+STATIN combination exhibit complementary and synergistic action
- ROVATITAN® is the single pill that proved a synergistic BP lowering effect compared to valsartan alone that is similar to valsartan + HCTZ combination
- ROVATITAN® showed a powerful LDL-C lowering effects that can be beneficial to patients who need high-intensity statin therapy
- ROVATITAN® can provide better efficacy to patients with diabetes
- ROVATITAN® is effective regardless of patient's characteristics
- ROVATITAN® has an excellent safety and tolerability profile in patients with hypertension and hyperlipidemia.
- Initial integrated therapy with ROVATITAN® can not only control BP & lipid profile but also CV events reductions as well

ROVATITAN®

Phase III clinical trials

1 + 1 > 2 !

SYNERGY

- Superior reduction on sitDBP
- Better efficacy for diabetes
- Powerful LDL-C lowering effect

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Thank you for your attention