Genetic testing in cardiovascular disease

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New Horizon Healthcare

Disclosures

- Speaker – Quest/Cleveland HeartLab

9p21

- “The heart attack gene”
- 9p21 is a region of the genome on the short arm of chromosome 9
- Considered the “most robust genetic marker of coronary artery disease” [1]
- Two SNPs associated with increased risk for CHD events
  - These two SNPs are highly correlated, with almost complete linkage disequilibrium
    - If one SNP has one mutated allele, it is highly likely the other SNP will have one mutated allele
- Biology of this region is not well understood
  - Contains elements that control gene transcription

(1.) Holdt LM, Teupser D. Recent studies of the human chromosome 9p21 locus, which is associated with atherosclerosis in human populations. *Arterioscler Thromb Vasc Biol*. 2012;32(2):196-206.

9p21-associated risk and frequency

Genotype*	Associated Risk	Population Frequency[1]
Noncarrier	No increased risk of early MI, AAA, or MI/CHD	27%
Heterozygous	25% increased risk MI/CHD 49% increased risk early MI 36% increased risk of AAA	50%
Homozygous	56% increased risk MI/CHD 102% increased risk early MI 74% increased risk of AAA	23%

**Genotypes for the rs10757278 and rs1333049 SNPs*
Due to high linkage disequilibrium, if one SNP is heterozygous the other is very likely to be heterozygous as well

(1.) Ivanova AA, Maksimov VN, Orlov PS, Ivanshchuk DE, Savchenko SV, Voevoda MI. Association of the genetic markers for myocardial infarction with sudden cardiac death. *Indian Heart J.* 2017;69 Suppl 1:S8-S11

9p21-associated risk is comparable to smoking and other accepted risk factors

Risk Factor and End Point	Heterozygous Carriers	Homozygous Carriers
9p21 and early MI[2]	1.5-fold	2.0-fold
Current smoker (vs. nonsmoker)[3]	2.0-fold	
9p21 and AAA[4]	1.4-fold	1.7-fold
9p21 and CHD / MI[2]	1.3-fold	1.6-fold
LDL-c (per SD increase)[5]	1.4-fold	
HDL-c (per SD decrease)*[5]	1.3-fold	
Age (per 5 years increase)[3]	1.2-fold	
Lp(a) (per 10 mg/dL increase)[3]	1.1-fold	

9p21 risk is independent of conventional risk factors for CAD[1]

**derived from a risk ratio of 0.71 per SD decrease*
Endpoint for all risk factors other than 9p21 in this table is CHD

(1.) Holdt LM, Teupser D. Recent studies of the human chromosome 9p21 locus, which is associated with atherosclerosis in human populations. *Arterioscler Thromb Vasc Biol*. 2012;32(2):196-206. (2.) Helgadottir A, Thorleifsson G, Manolescu A et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007;316:1491–93. (3.) Schaefer EJ, Lamon-Fava S, Jennifer JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men: The lipid research clinics coronary primary prevention trial. *JAMA* 1994;27:999–1003. (4.) Helgadottir A, Thorleifsson G, Magnusson KP et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet* 2008;40:217–24. (5.) The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993–2000.

9p21 improves risk assessment

- Which patients may benefit from the 9p21 risk SNPs test?
  - Patients who are of Caucasian, Chinese, Korean, Japanese, or East Indian descent with a family history of cardiovascular disease or who have traditional risk factors
  - The test may also be useful for risk stratification of those patients with diagnosed cardiovascular disease
- What does this test add to the risk profile of a patient?
  - This test has clinical utility in identifying those subgroups at higher genetic risk of cardiovascular disease, which may:
    - Allow for early detection and more aggressive monitoring, incorporation of lifestyle/behavioral changes, and treatment
    - Help guide therapy selection
    - Be of utility in family counseling

9p21 and population attributable risk (PAR)

- 9p21 has substantial PAR
- Although the risk levels associated with 9p21 are similar in magnitude to traditional risk factors, the PAR of 9p21 is substantial due to the high frequency of the risk-associated 9p21 variants
- Therefore, testing for 9p21 risk variants may have implications for early prevention of disease[1]

	Population Attributable Risk
9p21 and Early MI[2]	31%
9p21 and AAA[3]	26%
9p21 and CHD/MI[2]	21%

(1.) Roberts R. A customized genetic approach to the number one killer: coronary artery disease. *Curr Opin Cardiol* 2008;23:629–633 (2.) Helgadottir A, Thorleifsson G, Manolescu A et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007;316:1491–93. (3.) Helgadottir A, Thorleifsson G, Magnusson KP et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet* 2008;40:217–24.

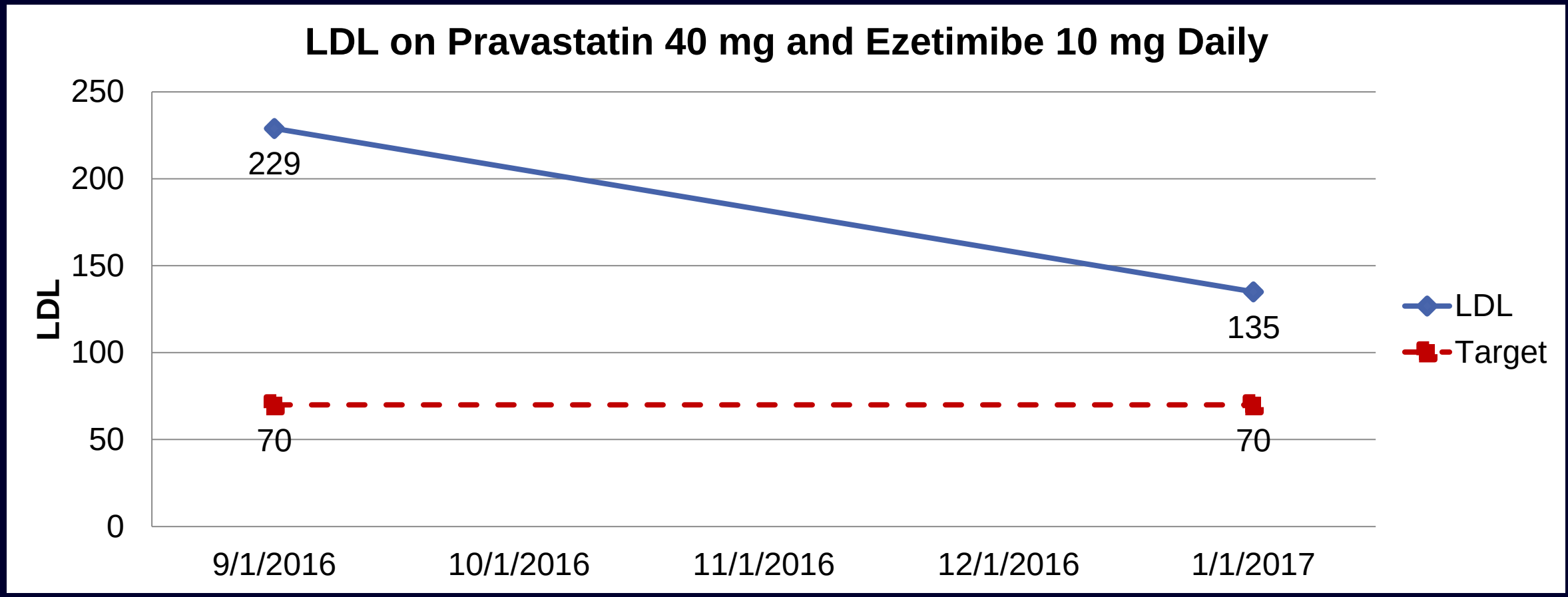
Jenny (61 y/o WF)

Homozygous Positive 9P21

Parameter	Value
Lp-PLA2 Activity	95 (normal < 75)
LDL	229
Sweat	2.3 gallons (estimate)

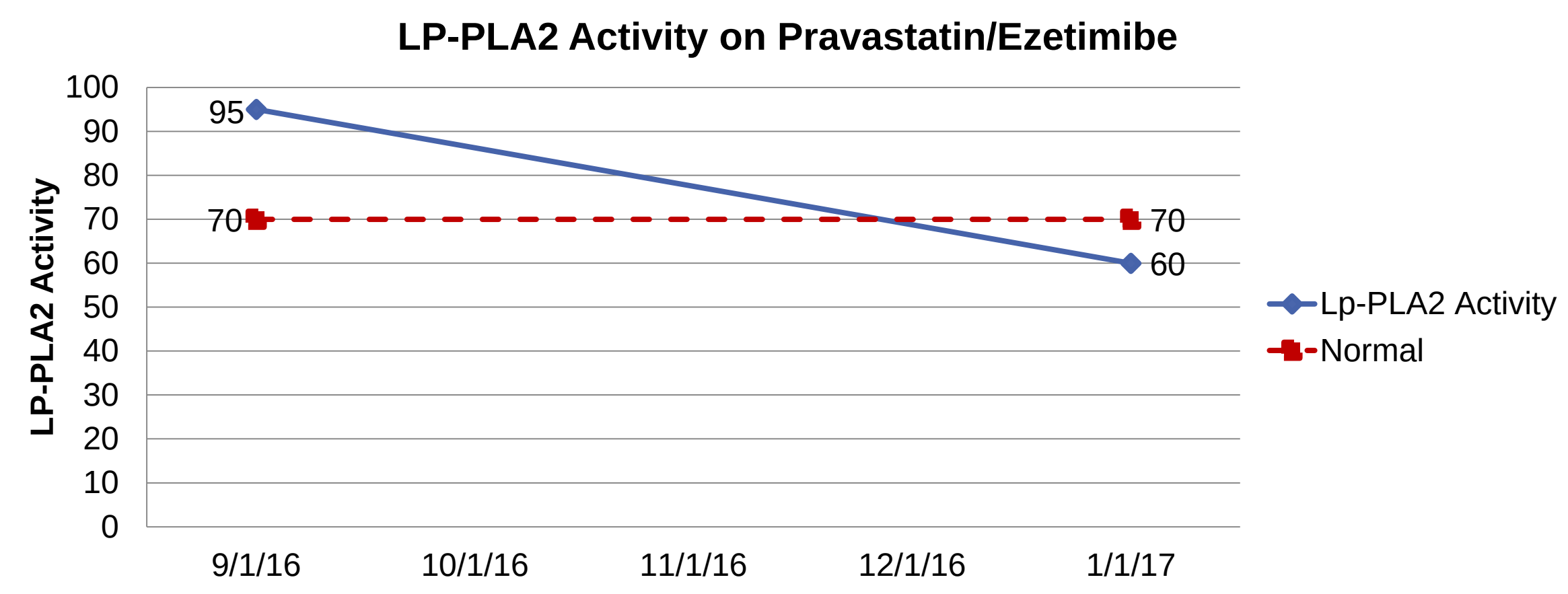
Jenny

Homozygous Positive 9P21



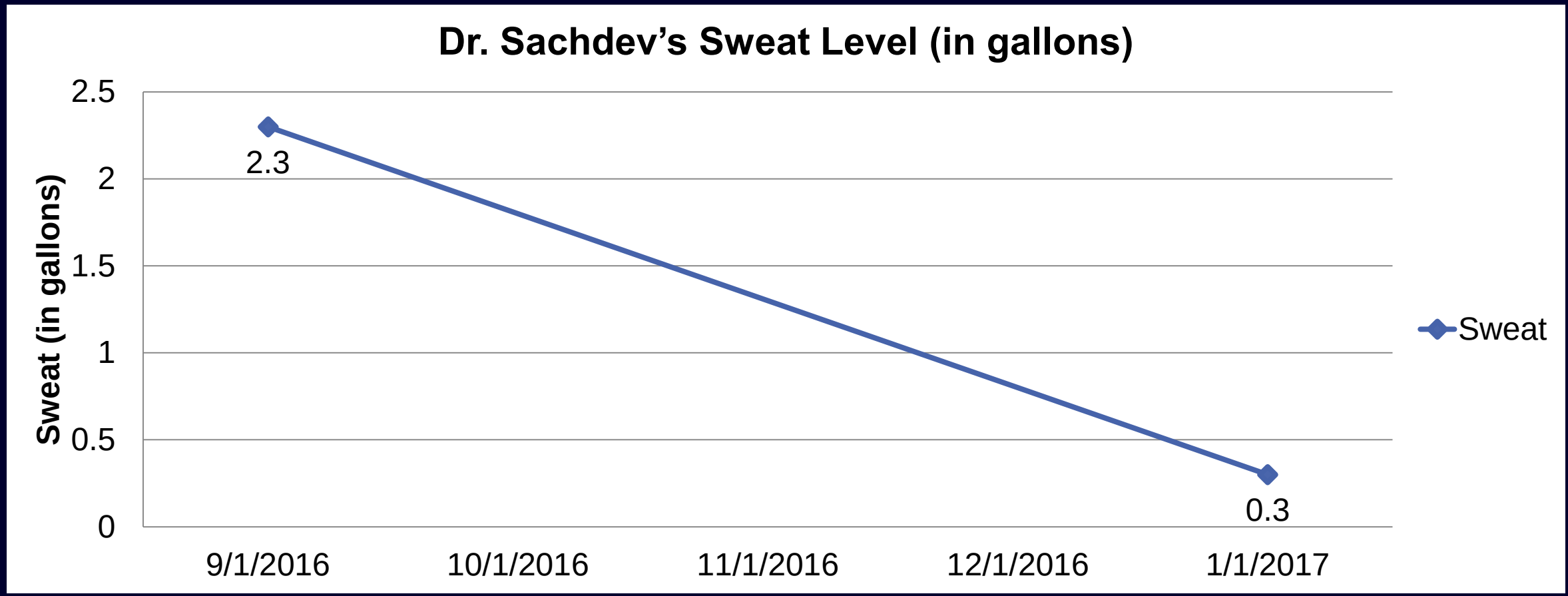
Jenny

Homozygous Positive 9P21



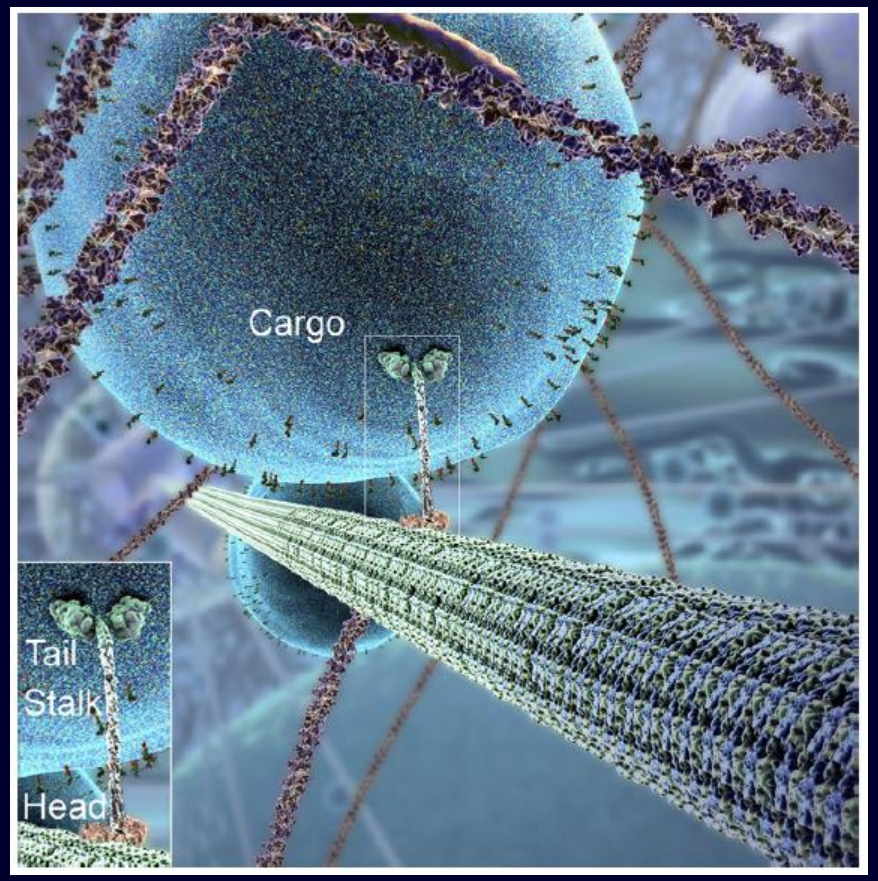
Jenny

Homozygous Positive 9P21



KIF6

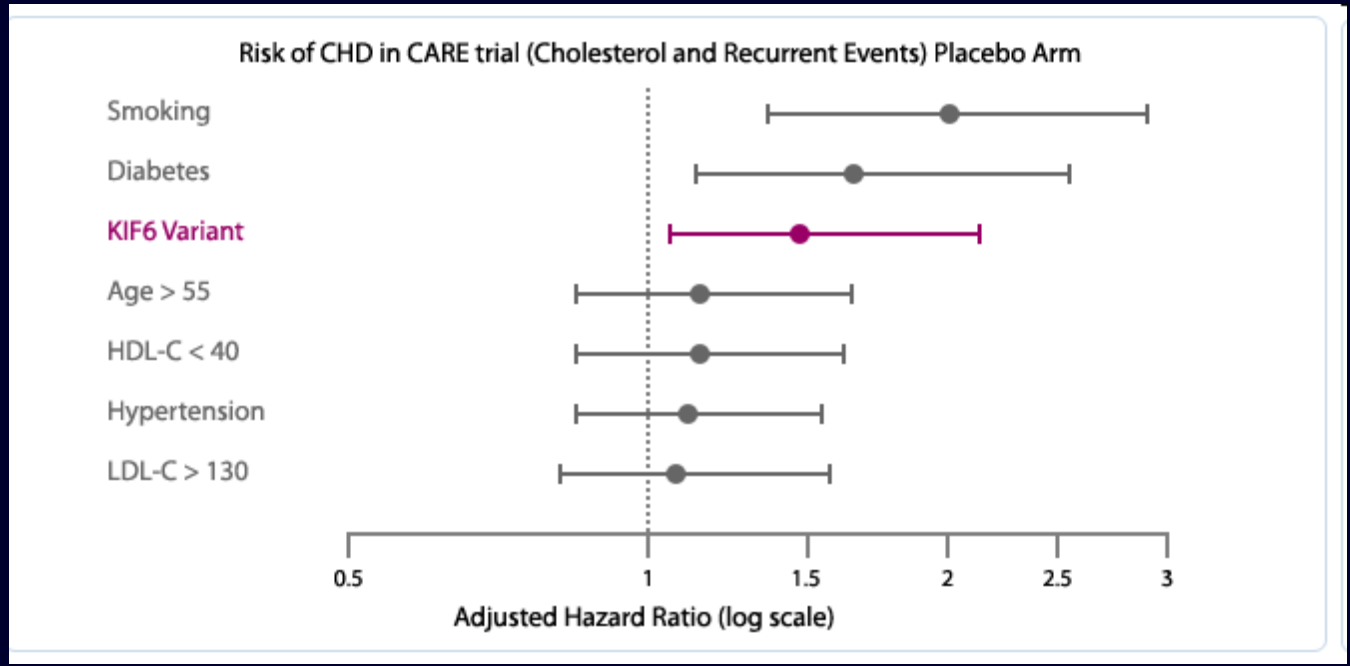
- One SNP in the *KIF6* gene associated with increased CHD risk and event reduction with statin therapy
- KIF6 is a member of the kinesin superfamily
  - Mediates the transportation organelles, proteins, and messenger RNA
  - Mutation at the SNP can effect function of the cargo-binding domain
  - Expressed in coronary arteries and vascular cells



Li Y, Iakoubova OA, Shiffman D, Devlin JJ, Forrester JS, Superko HR. KIF6 polymorphism as a predictor of risk of coronary events and of clinical event reduction by statin therapy. *Am J Cardiol*. 2010;106(7):994-8.

KIF6- associated CHD risk

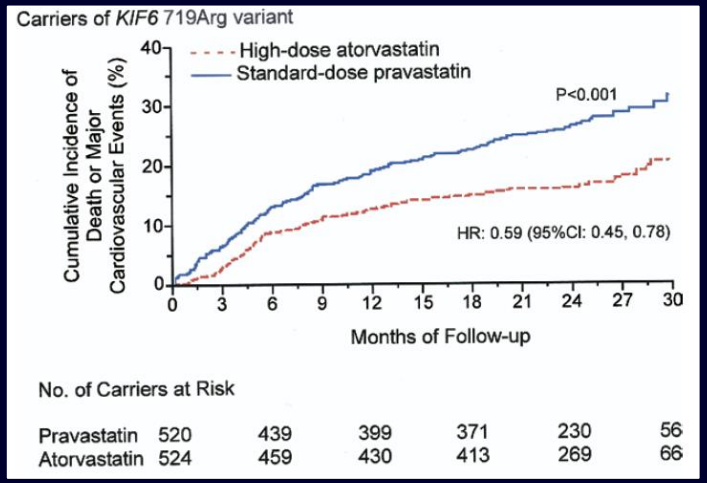
- Carriers: 55% greater CHD risk *independent* of other risk factors
  - Risk is reduced with 40mg pravastatin
    - NNT = 10 (PROVE-IT)
    - 40-60% RRR (CARE; WOS)
- Non Carriers: Risk defined by prevalence and severity of other risk factors
  - Minimal response to statins
    - NNT = 125 (PROVE-IT)
    - 6-20% RRR (CARE; WOS)

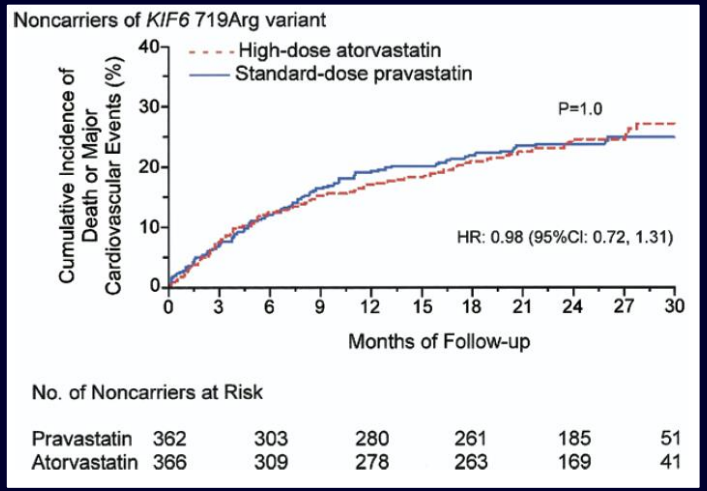


Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg Polymorphism in Kinesin-Like Protein 6 with Myocardial Infarction and Coronary Heart Disease in 2 Prospective Trials. *The CARE and WOSCOPS Trials. JACC.* 2008;51(4):435-443.

Atorvastatin reduces events more effectively in KIF6 carriers

- PROVE-IT-TIMI 22 Trial
  - 40 mg pravastatin vs 80 mg atorvastatin
  - Endpoint of death or major CVD events
  - Double-blind trial of ACS patients
  - N=1,778
  - Primarily middle-aged men with ACS in stable condition
  - Intensive statin therapy (80 mg atorvastatin) was found to reduce events more effectively in KIF6 carriers than in noncarriers
    - Relative risk reduction was 41% in KIF6 carriers and 6% in noncarriers
- NNT* was 25 for all patients (on atorvastatin)
  - NNT was 10 for KIF6 carriers with atorvastatin (vs. pravastatin)
  - NNT was 125 for noncarriers





Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2008;51(4):449-55.

Support for KIF6

- **CARE: Cholesterol and Recurrent Events[1]**
  - N=2,715
  - Secondary prevention in patients with a prior MI
  - 40 mg pravastatin vs placebo
- **WOSCOPS: West of Scotland Coronary Prevention Study[1]**
  - N=1,561
  - Primary prevention
  - 40 mg pravastatin vs placebo
- **ARIC: Atherosclerosis Risk in Communities[2]**
  - N=13,907
  - Population-based observational study; CHD endpoint
- **CHS: Cardiovascular Health Study[3]**
  - N=3,849
  - Population-based observational study; MI endpoint
- **WHS: Women's Health Study[4]**
  - N=25,283
  - Randomized, double-blind, placebo-controlled trial
  - Women > 45 years of age without previous history of CHD risk *independent* of other risk factors
- **PROVE-IT-TIMI 22 Trial[5]**
  - N=1,778
  - 40 mg pravastatin vs 80 mg atorvastatin
  - Double-blind trial of ACS patients; death or major CVD event endpoint

(1.) Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg Polymorphism in Kinesin-Like Protein 6 with Myocardial Infarction and Coronary Heart Disease in 2 Prospective Trials. *The CARE and WOSCOPS Trials. JACC.* 2008;51(4):435-443. (2.) Morrison AC, Bare LA, Chambless LE, et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2007;166(1):28-35. (3.) Shiffman D, O'meara ES, Bare LA, et al. Association of gene variants with incident myocardial infarction in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 2008;28(1):173-9. (4.) Shiffman D, Chasman DI, Zee RY, et al. A kinesin family member 6 variant is associated with coronary heart disease in the Women's Health Study. J Am Coll Cardiol. (5.)Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. J Am Coll Cardiol. 2008;51(4):449-55. 2008;51(4):444-8.

KIF6 summary and clinical implications

KIF6 Genotype	Associated Risk	Treatment Consideration	Population Frequency[1]
Carrier Arg/Arg or Trp/Arg	CHD risk increased up to 55%	Atorvastatin or pravastatin	60%
Noncarrier Trp/Trp	No increased CHD risk	--	50%

- KIF6 Noncarriers
  - No increased risk of CHD events
  - No significant event reduction from statin therapy
  - KIF6 noncarriers may still have standard risk factors that justify statin therapy
  - Clinicians may want to consider combination therapy with other drugs that have been proven to reduce CHD events.
- KIF 6 Carriers
  - Carriers are at increased CHD risk
  - Risk can be reduced with statin therapy, independent of LDL-C lowering
  - KIF6 helps clinicians provide patients with information about their CHD risk and individualized response to statin therapy

(1.) Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg Polymorphism in Kinesin-Like Protein 6 with Myocardial Infarction and Coronary Heart Disease in 2 Prospective Trials. *The CARE and WOSCOPS Trials. JACC.* 2008;51(4):435-443.

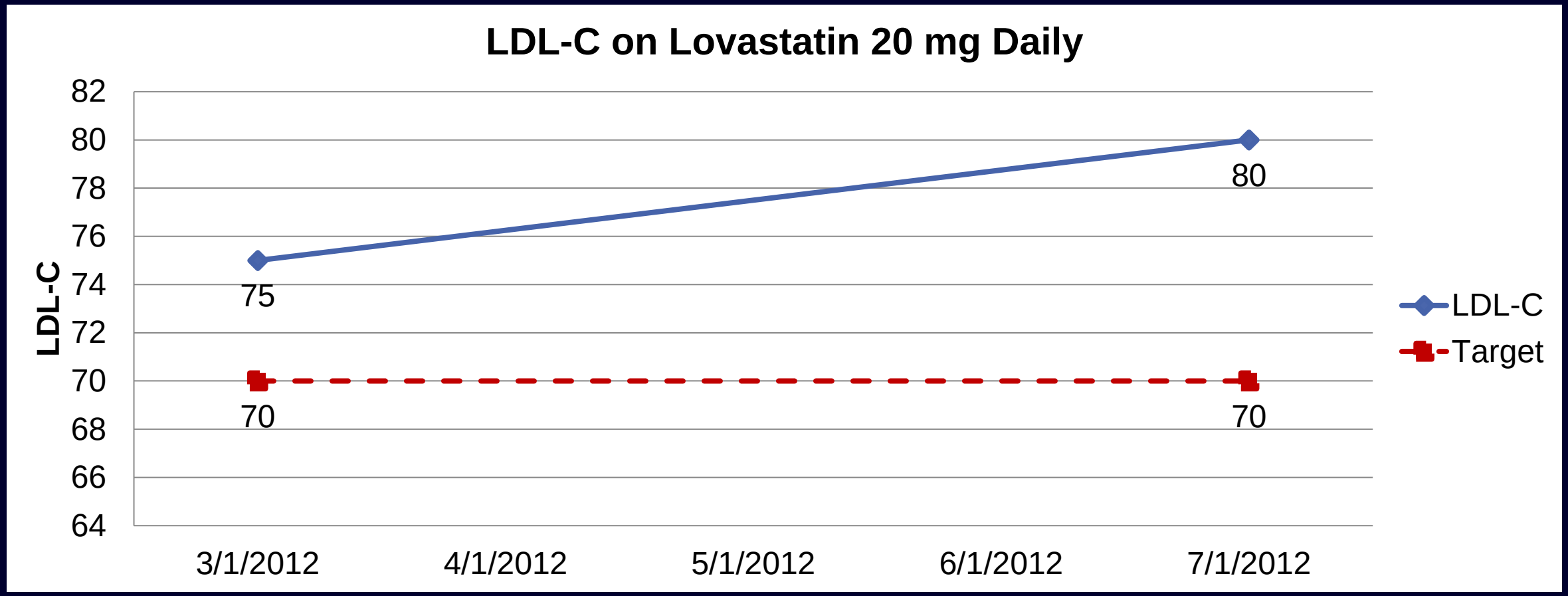
Sharon (72 y/o WF)

Homozygous Negative KIF-6 on Pravastatin 80 mg daily

Parameter	Value
Lp-PLA2	207 (normal < 200)
LDL	75
Pulse	140 bpm

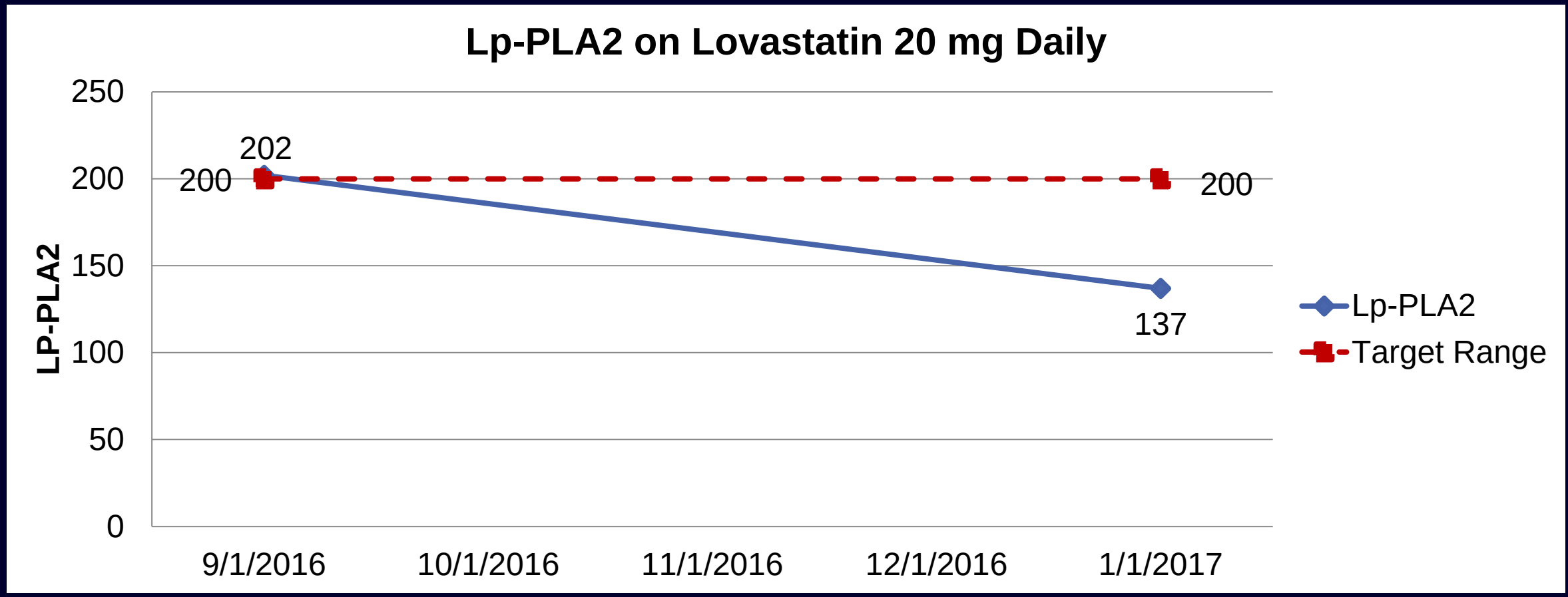
Sharon

Homozygous Negative KIF-6



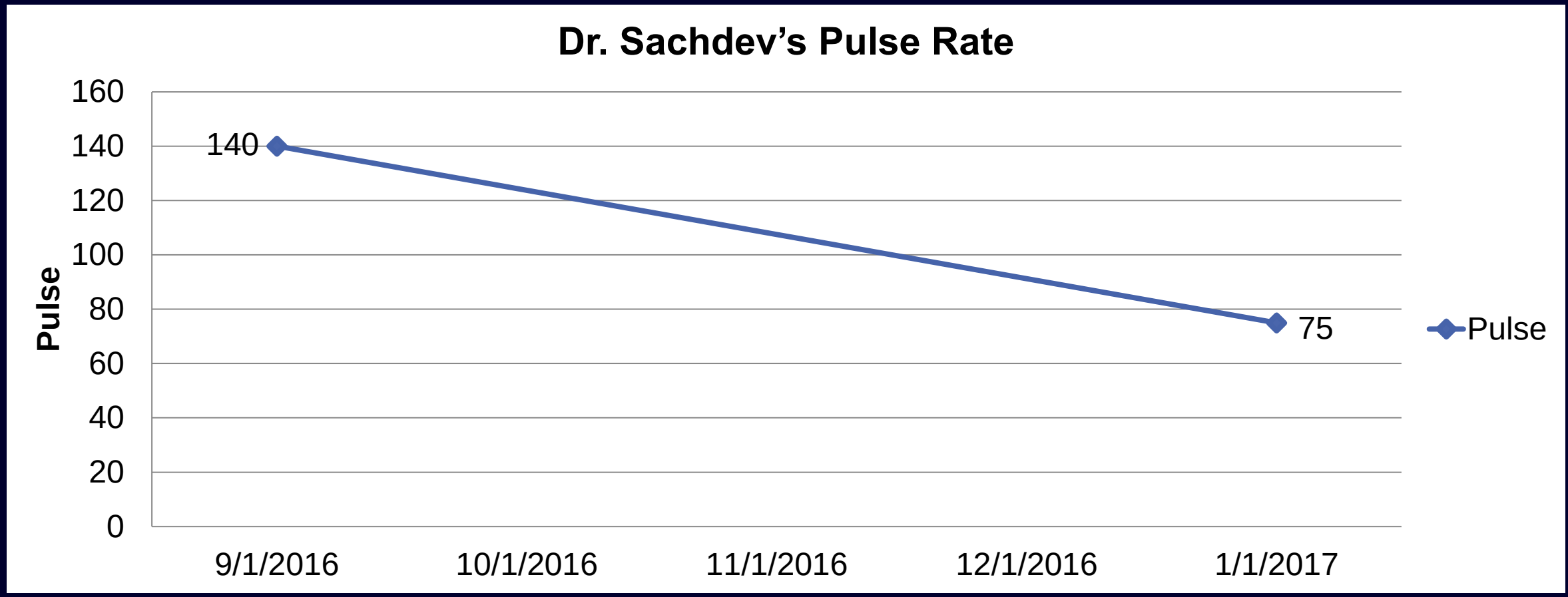
Sharon

Homozygous Negative KIF-6



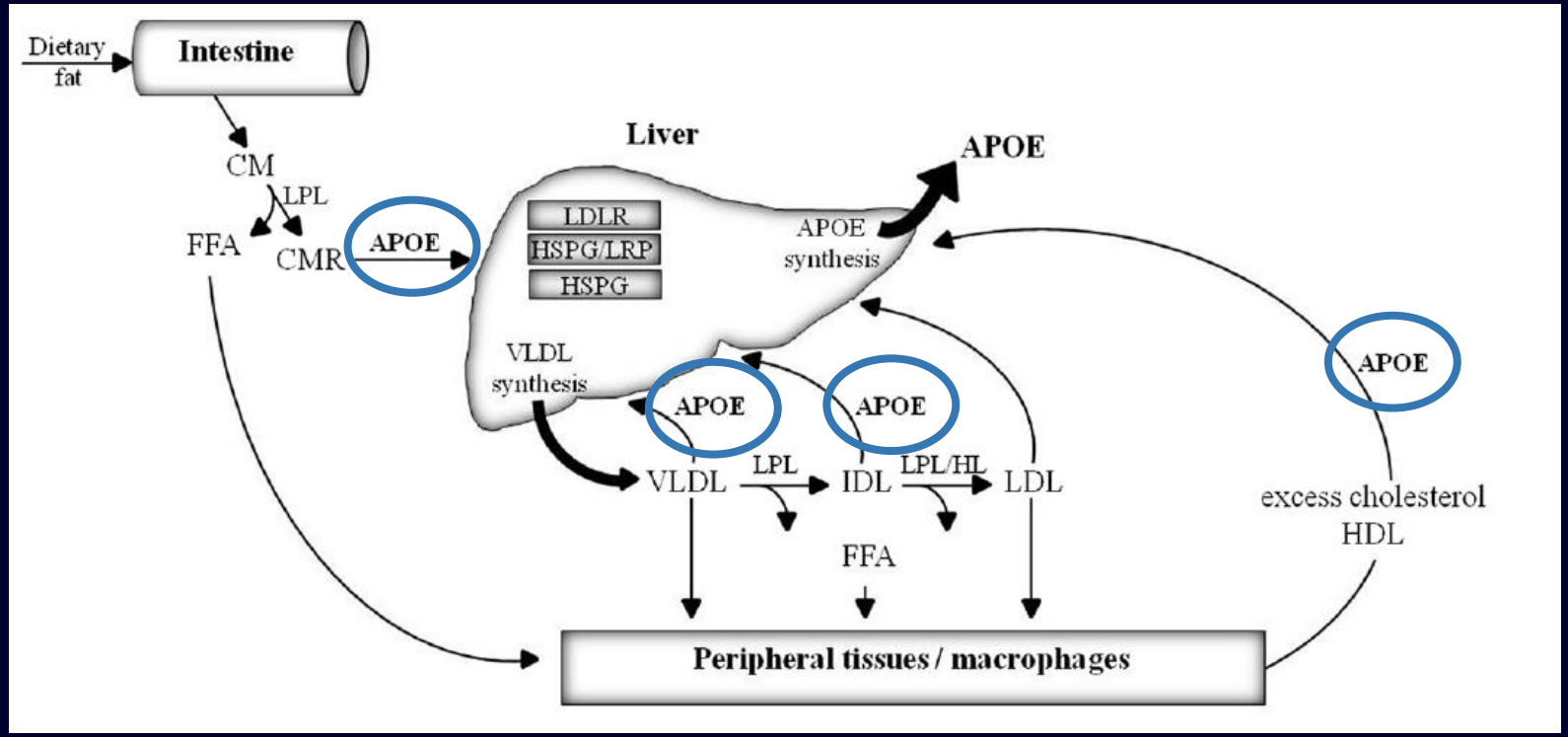
Sharon

Homozygous Negative KIF-6



The role of ApoE in lipid metabolism

- ApoE serves as the ligand to LDL receptors
- ApoE mediates the hepatic uptake of chylomicron remnants, very-low density lipoprotein, and intermediate density lipoproteins



Dose J, Huebbe P, Nebel A, and Rimbach G. *APOE* genotype and stress response – a mini review. *Lipids in Health and Disease*. 2016;15:121

3 ApoE isoforms and their effect on plasma lipids

- ApoE3 has average affinity for hepatic LDL-receptors (LDL-R)
  - No genotype impact
- ApoE2 has reduced affinity for LDL-R
  - Associated with slow conversion of IDL to LDL
  - Decreased LDL
  - Elevated triglycerides (TG)
- ApoE4 has increased affinity for LDL-R and limits HDL-binding
  - Inhibits normal cholesterol clearance process (reverse cholesterol transport or RCT)
  - Elevated total cholesterol, LDL, and TG
  - Decreased HDL

Mamotte CD, Sturm M, Foo JI, van Bockxmeer FM, Taylor RR. Comparison of the LDL-receptor binding of VLDL and LDL from ApoE4 and ApoeE3 homozygotes. *Am J Physiol.* 1999;276:E553-557.

ApoE-associated CVD risk

Genotype	Population Frequency[1]	CVD Risk	Treatment Consideration
2/2	1%	No increased risk[2] to slightly reduced risk[3]	Moderate fat diet (35%) if elevated triglycerides[4] Statin therapy[5]
2/3	10%		
2/4	2%		
3/3	62%	No increased risk[2]	Normal dietary modifications
3/4	20%	Increased risk (42%)[2]	Very low-fat diet (20%) if elevated LDL-C[6] Statin therapy[7]
4/4	5%		

(1) Eichner JE, Dunn ST, Perveen G et al. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *Am J Epidemiol*. 2002; 155: 487-495. (2) Song Y, Stampfer MJ, and Liu S. Meta-analysis: Apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med*. 2004; 141: 137-147. (3) Zhang Y, Tang HQ, Peng WJ, Zhang BB, and Liu M. Meta-analysis for the association of apolipoprotein E episilon2/epsilon3/epsilon4 polymorphism with coronary heart disease. *Chinese Med J.* 2015;218:1391-1398. (4) Moreno J, Perez-Jimenez F, Marin C et al. The effect of dietary fat on LDL size is influenced by apolipoprotein E genotype in healthy subjects. *J Nutr*. 2004; 134: 2517-2522. (5) Ordovas JM, Lopez-Miranda J, Perez-Jimenez F et al. Effect of apolipoprotein E and A-IV phenotypes on the low density lipoprotein response to HMG CoA reductase inhibitor therapy. *Atherosclerosis*. 1995; 113: 157-166. (6) Lopez-Miranda J, Ordovas JM, Mata P et al. Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *J Lipid Res*. 1994; 35: 1965-1975. (7) Nestel P, Simons L, Barter P et al. A comparative study of the efficacy of simvastatin and gemfibrozil in combined hyperlipoproteinemia: Prediction of response by baseline lipids, apo E genotype, lipoprotein(a) and insulin. *Atherosclerosis*. 1997; 129: 231-239.

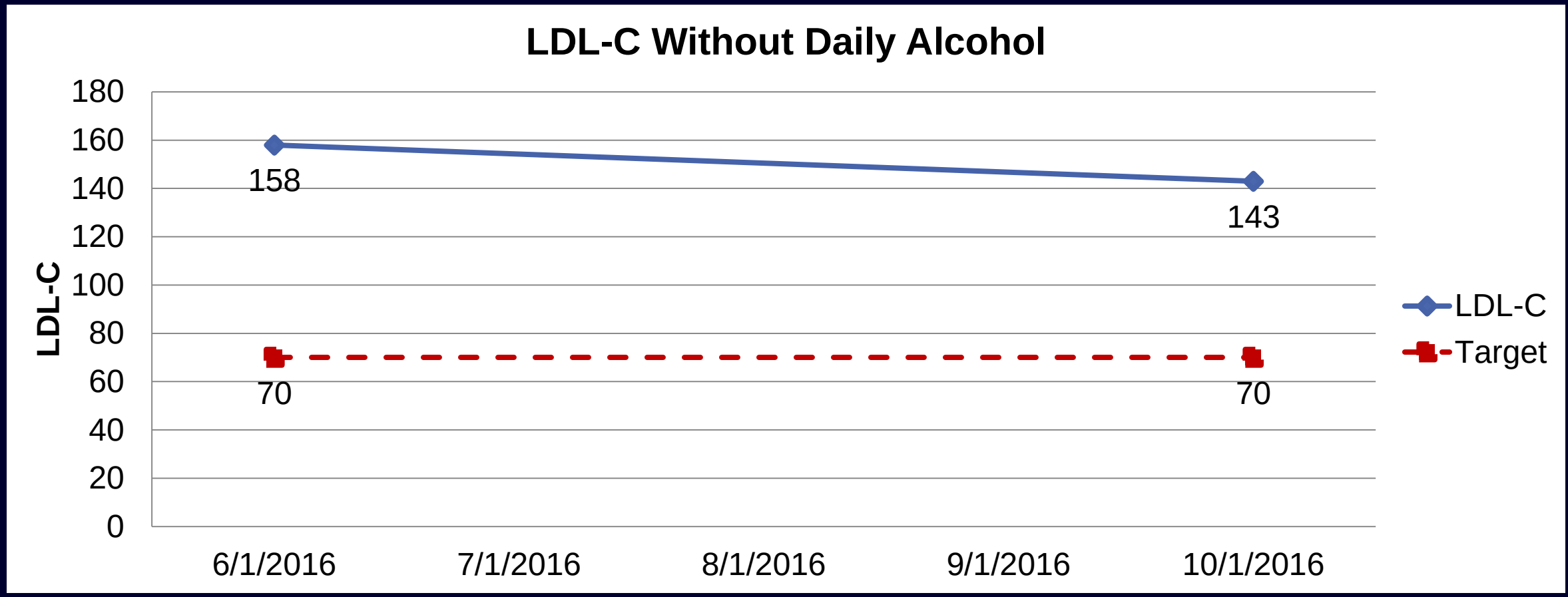
Ricky (38 y/o WM)

Apo E 3/4 Drinking Red Wine Daily

Parameter	Value
Lp-PLA2 Activity	93 (normal < 75)
LDL	158
LDL-P	1983
Alcohol Intake	1-2 glasses wine/day

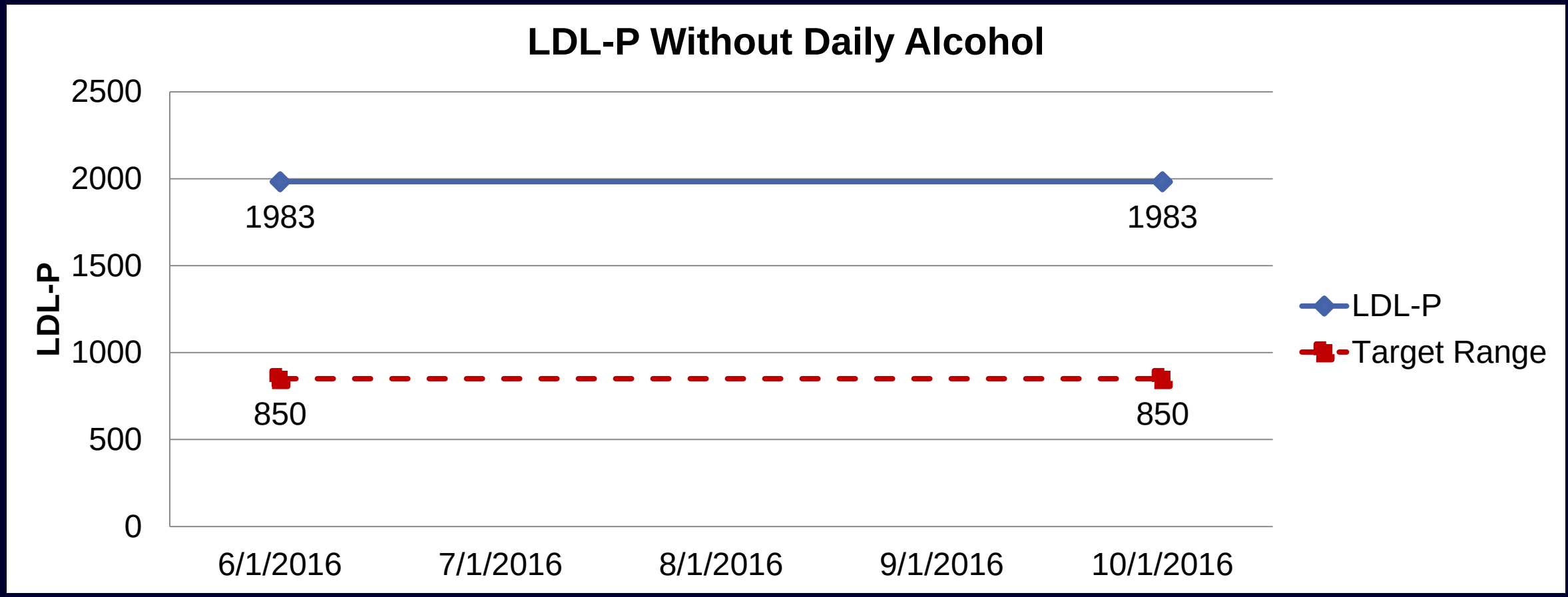
Ricky

ApoE 3/4 on No Alcohol



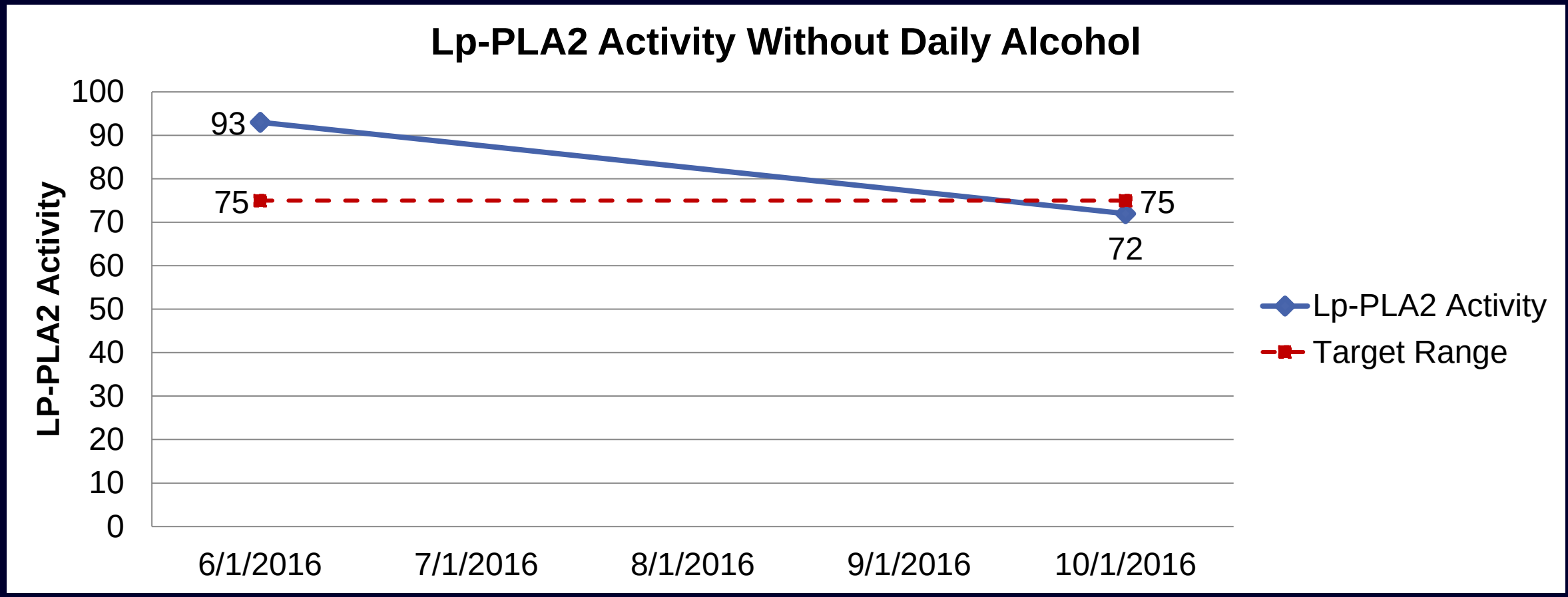
Ricky

ApoE 3/4 on No Alcohol



Ricky

Apo E 3/4 No Alcohol



Other Useful Genetic Tests

The Genetic Toolbox

- 4q25: Atrial Fibrillation Risk
- IL-1: Heightened Response to Inflammation
- Haptoglobin: CV Risk in Diabetics
- LPA Aspirin: CV Risk and Aspirin Response
- LPA-Intron 25: Independent Risk Factor for CV Disease related to LP(a)
- And More…..


The End