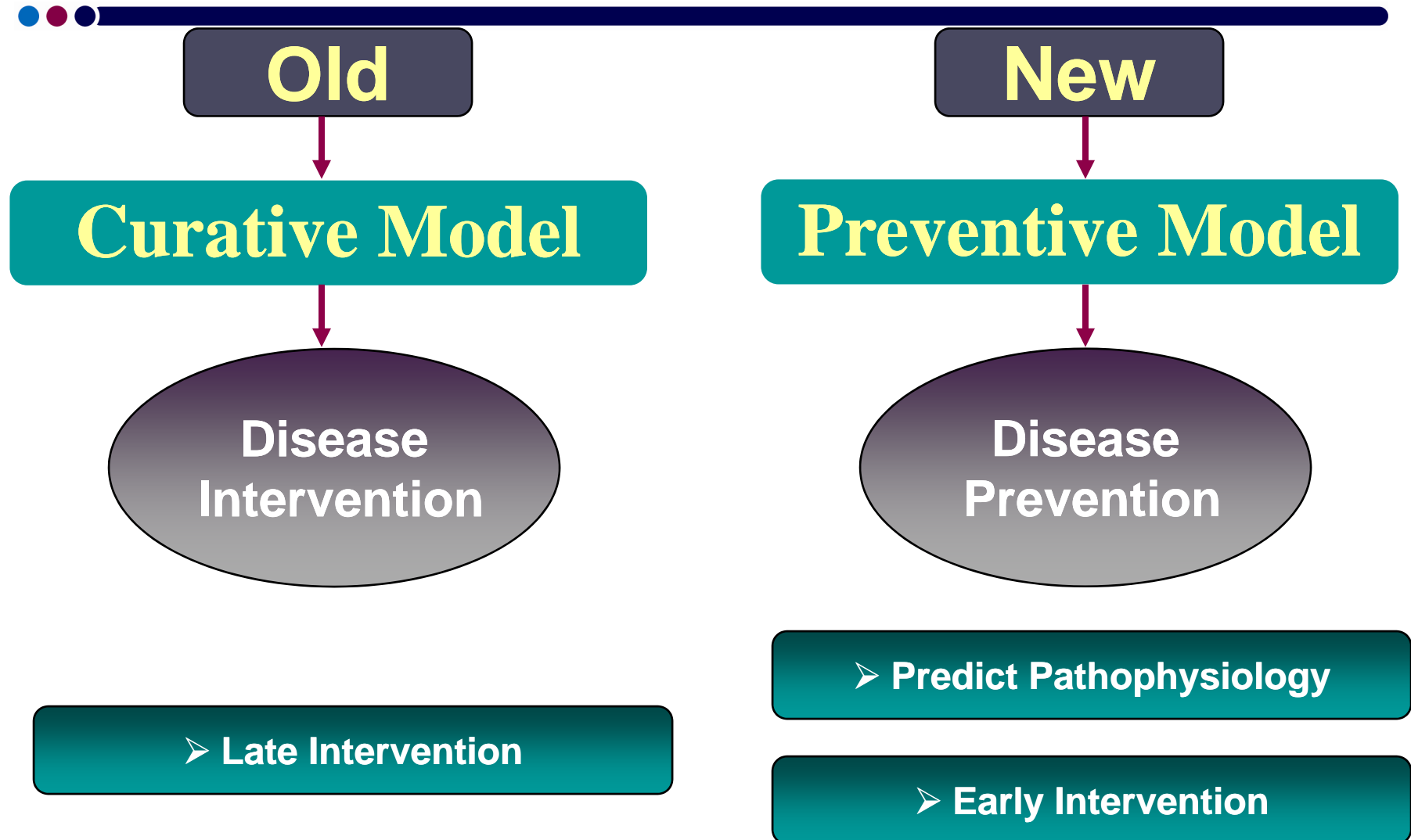


# **BHL Advanced Lipid Testing Case Study Presentation**

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# CVD Management — Paradigm Shift



# Berkeley Provides Insight into Other CVD Risk Factors

- LDL Lipoproteins

- LDL-C
- LDL-S<sub>3</sub>GGE™
- ApoB and ApoB Ultra
- Q-LDL
- Lp(a)

- HDL Lipoproteins

- HDL-C
- HDL-S<sub>10</sub>GGE™

- TG

- Insulin

- Inflammation

- Lp-PLA2
- hs-CRP
- Fibrinogen
- Homocysteine

- Genetic Testing

- Apo E Genotype
- KIF6



# Elevated LDL-C

## *Treatment Considerations*

Lifestyle Changes	Pharmacology
<ul style="list-style-type: none"><li>• <b>Fat restricted, cardioprotective diet</b></li><li>• <b>Weight loss</b></li><li>• <b>Regular exercise</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Primary lipid-lowering drug</b> <b>Statins</b></li> <li>• <b>Additional lipid-lowering drugs</b><ul style="list-style-type: none"><li>• <b>Bile acid sequestrants</b></li><li>• <b>Cholesterol absorption inhibitors</b></li><li>• <b>Nicotinic acid (Niacin)</b></li><li>• <b>Fibrates</b></li></ul></li></ul>

Berkeley HeartLab, Inc., Physician Reference Binder, 2008.

Berkeley HeartLab, Inc., Clinical Implications Manual, 2006.

Stone, Neil & Conrad Blum, Management of Lipids in Clinical Practice, 6<sup>th</sup> ed.

# Low HDL-C

## Treatment Considerations

Lifestyle Changes	Pharmacology	Other
<ul style="list-style-type: none"> <li>• Fat restricted, cardioprotective diet</li> <li>• Weight loss</li> <li>• Regular exercise</li> <li>• Smoking cessation</li> </ul>	<p><b>Primary HDL-C raising pharmacology</b></p> <ul style="list-style-type: none"> <li>• Nicotinic acid (Niacin)</li> <li>• Fibrates</li> </ul> <p><b>Additional HDL-C raising pharmacology</b></p> <ul style="list-style-type: none"> <li>• Thiazolidinediones (TZDs)</li> <li>• Statins (minor effect)</li> <li>• Omega-3 fish oil</li> </ul>	<ul style="list-style-type: none"> <li>• Correct insulin resistance</li> <li>• Note: Moderate alcohol intake raises HDL3</li> </ul>

Berkeley HeartLab, Inc., Physician Reference Binder, 2008.

Berkeley HeartLab, Inc., Clinical Implications Manual, 2006.

Stone, Neil & Conrad Blum, Management of Lipids in Clinical Practice, 6<sup>th</sup> ed.

# TGs

## Treatment Considerations

Lifestyle Changes	Pharmacology
<p><b>Focus on primary lifestyle changes (dietary modifications &amp; increased exercise) for borderline-high TG elevations</b></p> <ul style="list-style-type: none"><li>• Exercise leads to better cellular energy utilization by body tissues (lower TG &amp; increase HDL)</li><li>• Exercise decreases diabetic insulin requirements</li><li>• Exercise lowers TG (&amp; LDL-C) even in absence of wt loss</li></ul>	<p><b>Primary TG reduction pharmacology</b></p> <ul style="list-style-type: none"><li>• Nicotinic acid (Niacin)</li><li>• Fibrates</li><li>• Omega-3 fish oil</li></ul> <p><b>Additional TG reductio pharmacology</b></p> <ul style="list-style-type: none"><li>• Thiazolidinediones (pioglitazone not rosiglitazone)</li><li>• Statins (modest effect)</li><li>• Avoid alcohol (alcohol reduces beta-oxidation of fatty acids)</li><li>• Very high TG levels ( &gt; 500 mg/dL) require treatment to prevent acute pancreatitis</li></ul>


Berkeley HeartLab, Inc., Physician Reference Binder, 2008.

Berkeley HeartLab, Inc., Clinical Implications Manual, 2006.

Stone, Neil & Conrad Blum, Management of Lipids in Clinical Practice, 6<sup>th</sup> ed.

# ApoB

## Treatment Considerations



Lifestyle Changes	Pharmacology
<ul style="list-style-type: none"><li>• Fat restricted, cardioprotective diet</li><li>• Weight loss</li><li>• Regular exercise</li></ul>	<p><b>Primary lipid-lowering pharmacology Statins</b></p> <p><b>Additional lipid-lowering pharmacology</b></p> <ul style="list-style-type: none"><li>• Bile acid sequestrants</li><li>• Cholesterol absorption inhibitors</li><li>• Nicotinic acid (Niacin)</li><li>• Fibrates</li></ul> <p><b>Combination therapy with statins &amp; nicotinic acid &amp;/or fibrates can be effective in pts with high apoB &amp; small dense LDL disorder</b></p>

Zambon A et al. Circulation 1999 April 20;99(15):1959-64.

Sniderman AD et al. CMAJ 2001 January 9;164(1):44-7.

# LDL-S<sub>3</sub>GGE

## Treatment Considerations

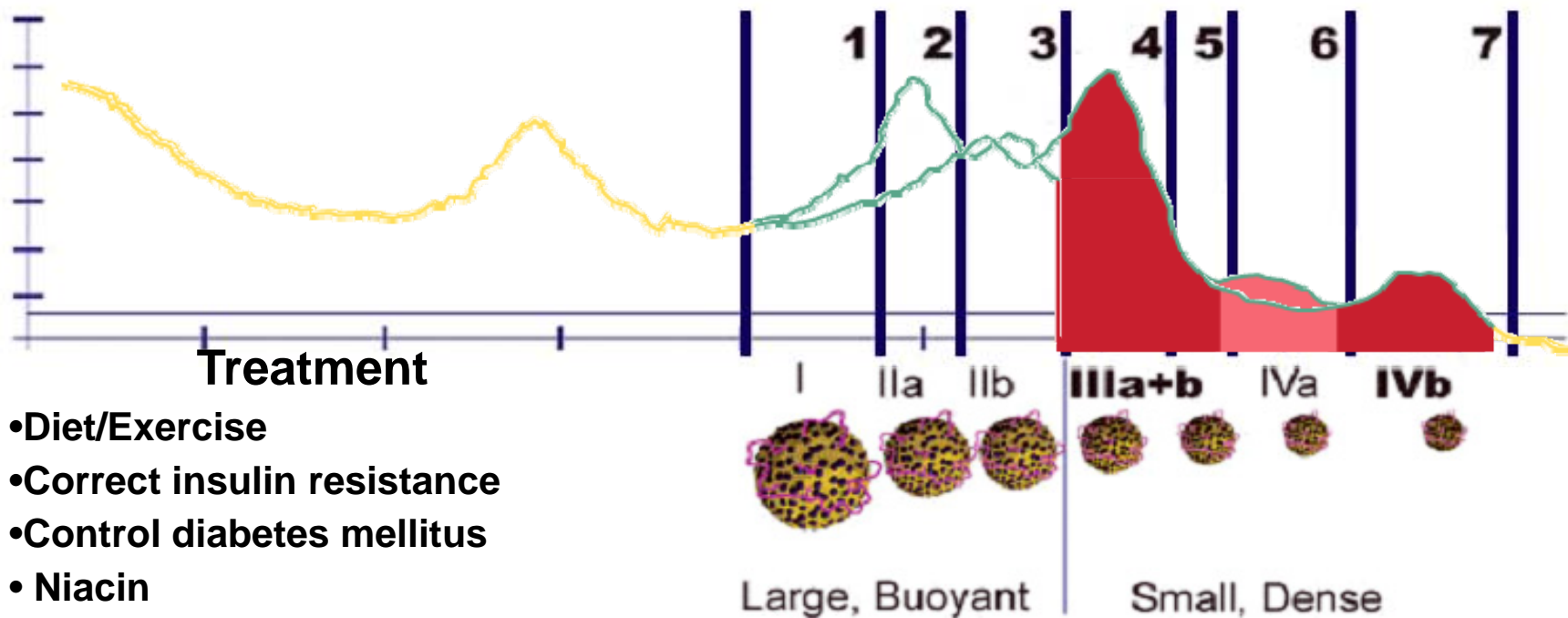
Lifestyle	Pharmacology	Other
<ul style="list-style-type: none"><li>• Fat restricted, cardioprotective diet</li><li>• Weight loss</li><li>• Regular exercise</li><li>• Smoking cessation</li></ul>	<p><b>Primary small dense LDL-lowering pharmacology</b></p> <ul style="list-style-type: none"><li>• Nicotinic acid (Niacin)</li><li>• Fibrates</li></ul> <p><b>Additional small dense LDL-lowering pharmacology</b></p> <ul style="list-style-type: none"><li>• Thiazolininediones (TZDs)</li><li>• Statins (minor effect)</li><li>• Omega-3 fish oil</li></ul>	<ul style="list-style-type: none"><li>• Correct insulin resistance</li><li>• Control diabetes mellitus</li><li>• Higher total combined % of 4 atherogenic small LDL particle subclasses (IIIa + IIIb + IVa + IVb) determines aggressiveness of treatment</li></ul>

Berkeley HeartLab, Inc., Physician Reference Binder, 2008.

Berkeley HeartLab, Inc., Clinical Implications Manual, 2006.

# Monitoring Treatment – *Attacking Small Dense LDL Particles*

## LDL-S<sub>3</sub>GGE™



- Diet/Exercise
- Correct insulin resistance
- Control diabetes mellitus
- Niacin
- Fibrates
- TZDs (off label)
- Statins +/-
- Omega-3 fish oil

# Lp(a)

## Treatment Considerations

Goals	Diet & Exercise	Niacin	Fibrate	Statin	Estrogen
<b>Primary Goal:</b> Decrease Lp(a) to < 30 mg/dL	NA	Niaspan 2,000 mg* (Mean ↓ of 24%)**  Niacin IR 3,000 mg (Mean ↓ of 36 %)**	+/-	NA  May ↑ Lp(a) in some pts	Mean ↓ * 20-30%

**\*If unable to achieve Lp(a) goal, significantly ↓ LDL-C & Apo B**

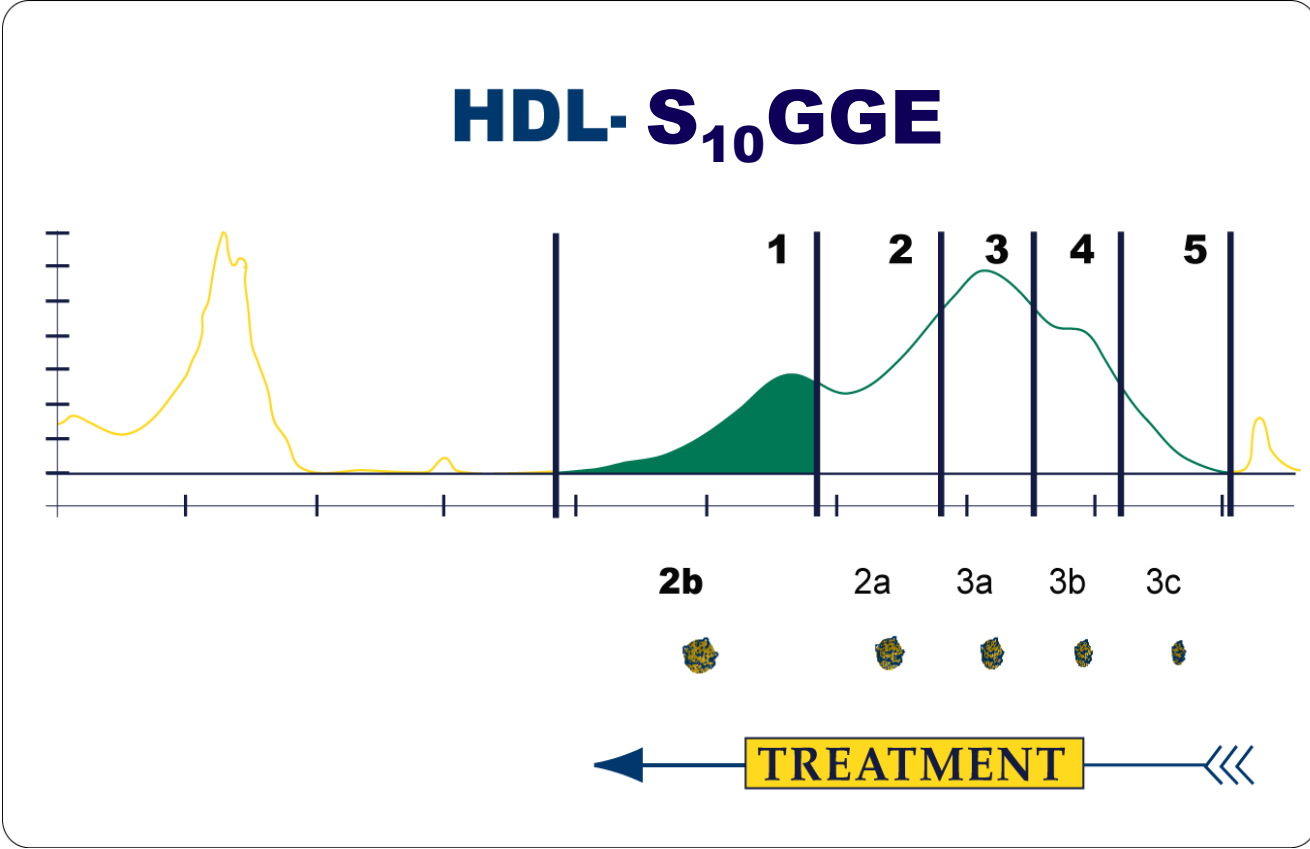
**\*\*Effects of treatment may not be seen for a year or more  
 Lp(a) very resistant to treatment response**

Kostner GM et al. Circulation 1989;80:1313-1319.

Utermann G. Science, 1989;246:904-910.

# HDL-S<sub>10</sub>GGE

## Analysis



### HDL Subclass Treatment Options

- Diet
- Weight Loss
- Regular Exercise
- Smoking Cessation
- Nicotinic Acid
- Fibrates
- Nicotinic Acid plus Statin

# Lp-PLA<sub>2</sub>

## Treatment Considerations

Associated Treatment Goals	Pharmacology
<p><b>Control Blood Pressure</b></p> <ul style="list-style-type: none"><li>• Antihypertensives</li></ul> <p><b>Optimize Lipid Levels</b></p> <ul style="list-style-type: none"><li>• ↓ LDL-C to 100 mg/dL intermediate risk pts</li><li>• ↓ LDL-C to 70 mg/dL in high risk pts</li></ul> <p><b>Control other CV risk markers i.e. Lp(a) &amp; small, dense LDL</b></p> <p><b>Diet &amp; Exercise</b></p>	<p><b>Therapy that reduces Lp-PLA<sub>2</sub> levels</b></p> <ul style="list-style-type: none"><li>• Statin</li><li>• Fenofibrate</li><li>• Nicotinic acid</li></ul> <p><b>Addition of nicotinic acid therapy to well-controlled statin therapy results in cumulative further reduction in Lp-PLA<sub>2</sub></b></p>

Tsimihodimos et al. Arterioscler Thromb Vasc Biol 2002 February 1;22(2):306-11.

Tsimihodimos et al. J Lipid Res 2003 May;44(5):927-34.

# hs-CRP

## *Treatment Considerations*

Lifestyle Changes	Pharmacology
<ul style="list-style-type: none"><li>• <b>Fat restricted, cardioprotective diet</b></li><li>• <b>Weight loss</b></li><li>• <b>Regular exercise</b></li><li>• <b>Smoking cessation</b></li></ul>	<p><b>Primary pharmacology</b></p> <ul style="list-style-type: none"><li>• <b>Statins</b></li></ul> <p><b>Additional pharmacology</b></p> <ul style="list-style-type: none"><li>• <b>Nicotinic acid (Niacin)</b></li><li>• <b>Fibrates</b></li><li>• <b>Aspirin</b></li><li>• <b>Platelet aggregation inhibitors</b></li><li>• <b>Angiotensin converting enzyme inhibitors (ACEI)</b></li><li>• <b>Angiotensin receptor blockers (ARBs)</b></li><li>• <b>Some beta blocking agents</b></li><li>• <b>TZDs</b></li><li>• <b>Celebrex</b></li></ul>

# Obesity

- Relationship of obesity to a cascade of risk factors
- Obesity
- Insulin resistance in conjunction with:
  - Elevated blood pressure
  - Inflammation (Elevated CRP)
  - Increased insulin
  - Increased Glucose and DM
  - Increased TG
  - Increase small dense LDL
  - Low HDL
  - Increased coaguability
  - Contributing to endothelial dysfunction
  - Leading to atherosclerosis
- Brown, V et al. Albert Einstein College of Medicine.2005

# Insulin

## *Treatment Considerations*

Increase Insulin Sensitivity	Focus on Primary Lifestyle Changes
<ul style="list-style-type: none"><li>• <b>Increase muscle mass by muscular exercise &amp; regular physical activity</b></li><li>• <b>Decrease visceral adiposity to decrease fat soluble stores, decrease adipose cell leptin output &amp; increase adiponectin production</b></li></ul>	<ul style="list-style-type: none"><li>• <b>Fat restricted, cardioprotective diet containing complex carbohydrates &amp; poly-unsaturated fatty acids</b></li><li>• <b>Decrease total insulin requirement by following a reduced simple carbohydrate intake &amp; increase fiber intake</b></li><li>• <b>Regular exercise program</b></li><li>• <b>Weight loss with a target BMI of ~ 25 kg/m<sup>2</sup></b></li></ul>

Berkeley HeartLab, Inc., Physician Reference Binder, 2008.

Berkeley HeartLab, Inc., Clinical Implications Manual, 2006.

# Insulin

## *Treatment Considerations cont*

Pharmacologic Methods of Meeting Insulin Requirements or Regulating Insulin Sensitivity	
Drug	Mode of Action
<ul style="list-style-type: none"><li>•Alpha glucosidase inhibitors (acarbose)</li><li>•Sulfonylureas (glipizide or glyburide)</li><li>•Biguanides (metformin)</li><li>•PPAR agonists Fibrates (fenofibrates) Thiazoladinediones (TZDS) rosiglitazone or pioglitazone</li></ul>	<ul style="list-style-type: none"><li>•Decreases intestinal absorption of CHO</li><li>•Increase pancreatic islet cell secretion of insulin</li><li>•Decrease hepatic glycogenolysis &amp; gluconeogenesis</li><li>•Increase insulin sensitivity for cell membrane glucose transport</li></ul>

# KIF6

## Definition

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- KIF6 is a genetic test for the Trp719Arg single nucleotide polymorphism (SNP) run on DNA extracted from whole blood
- KIF6 is a member of the family of proteins called kinesins
  - Kinesins transport molecules within the cell from one part of the cell to the other
    - Kinesins move molecules by “walking” on a microtubule within a cell
  - Transported molecules are called cargo
    - Examples of cargo: Organelles, protein complexes, mRNA & lipids
- A SNP is a variation in the sequence of a gene that occurs when one nucleotide is altered
  - This results in altered structure & function of the gene product

# KIF6

## Interpretation of Results

- The genotype for a KIF6 Carrier (60% of the population) will have an Arg allele (e.g., Arg719Trp or Arg719Arg)
- The genotype for a KIF6 Noncarrier (40% of the population) will lack the Arg allele (e.g., Trp719Trp).

<i>Patient Report KIF6 results</i>	<i>CVD Risk Characterization</i>	<i>Clinical Abnormality Summary</i>
Arg/Arg	<b>Increased Risk</b>	KIF6 Genotype: 719 Arg/Arg homozygous <b>Carrier of the KIF6 719Arg allele</b>
Trp/Arg	<b>Increased Risk</b>	KIF6 Genotype: 719 Trp/Arg heterozygous <b>Carrier of the KIF6 719Arg allele</b>
Trp/Trp	<b>Normal Risk</b>	KIF6 Genotype: 719 Trp/Trp homozygous <b>Noncarrier of the KIF6 719Arg allele</b>

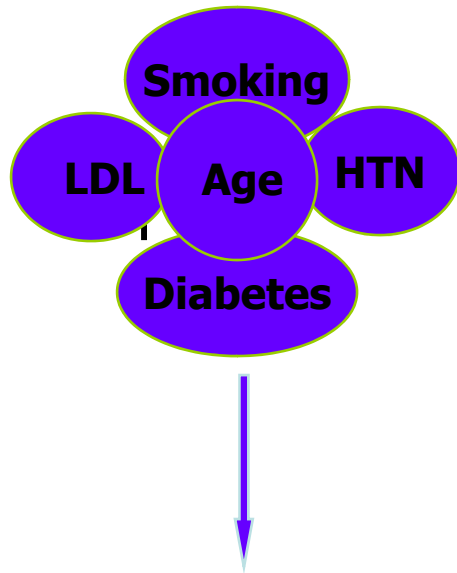
# KIF6

## Treatment Considerations

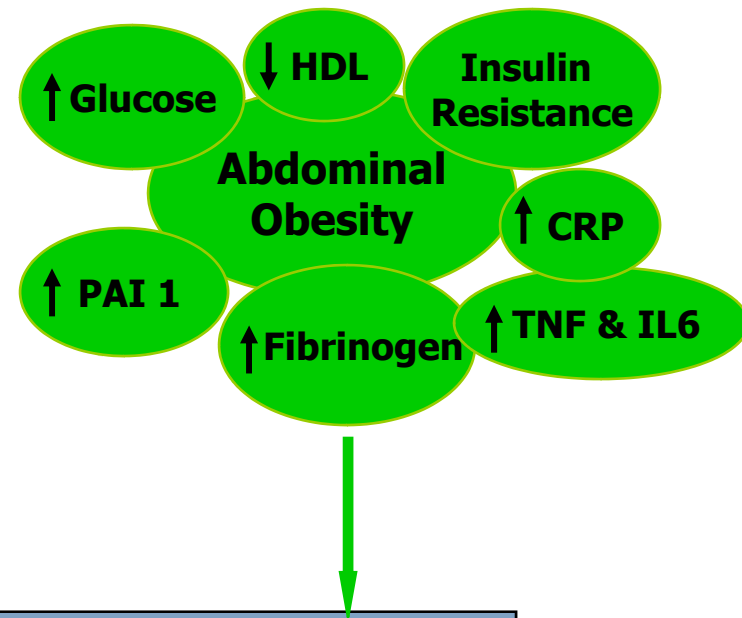
<b>Treatment</b>	<b>Carriers</b> (Arg/Arg,Arg/Trp)	<b>NonCarriers</b> (Trp/Trp)
• <b>Statin</b>	•Life-long statin treatment essential •For pts with high CHD risk, active CHD or ACS maximally tolerated dose should be used	•Statin is important but combination therapy recommended for more event risk reduction
• <b>Combination Therapy</b>	•Combination therapy important but statin therapy has shown to be a powerful event risk reducer	•Combination therapy is highly recommended (considering the less than average event risk reduction from statins)
• <b>Lifestyle Changes</b>	•Lifestyle changes are important	•Lifestyle changes are more important (considering the less than average event risk reduction from statins)

# Cardiometabolic Risk Update from ACC - 2006

## Traditional Risk Factors



## Emerging Risk Factors



+

Leads to Increased Cardiovascular disease Risk

"We need to include these newer risk factors in our routine assessment." Sidney C. Smith, MD

# Apo E Genotype — Metabolic Expression of Environmental Factors

	Apo E2 Response		Apo E3 Response		Apo E4 Response	
Genotype	2/2	2/3	3/3	2/4	3/4	4/4
Population Frequency	1%	10%	62%	2%	20%	5%
Fish Oil <sup>1</sup>	↓↓ TG ↓ small dense LDL ↑ HDL		↓ TG ↓ small dense LDL ↑ HDL		↓ TG ↓↓ small dense LDL ↓ HDL ↑↑ LDL	
Low Fat Diet <sup>2,3</sup>	↓ LDL ↑ small dense LDL		↓↓ LDL ↔ small dense LDL		↓↓↓ LDL ↓ small dense LDL	
Moderate Fat Diet <sup>3</sup>	↔ LDL ↔ small dense LDL		↓ LDL ↓ small dense LDL		↓ LDL ↑↑ small dense LDL	
Moderate Alcohol <sup>4</sup>	↑ HDL ↓ LDL		↑ HDL		↓ HDL ↑ LDL	
Effective Drug Response	Atorvastatin Pravastatin Lovastatin		No distinction		Probucol Simvastatin	

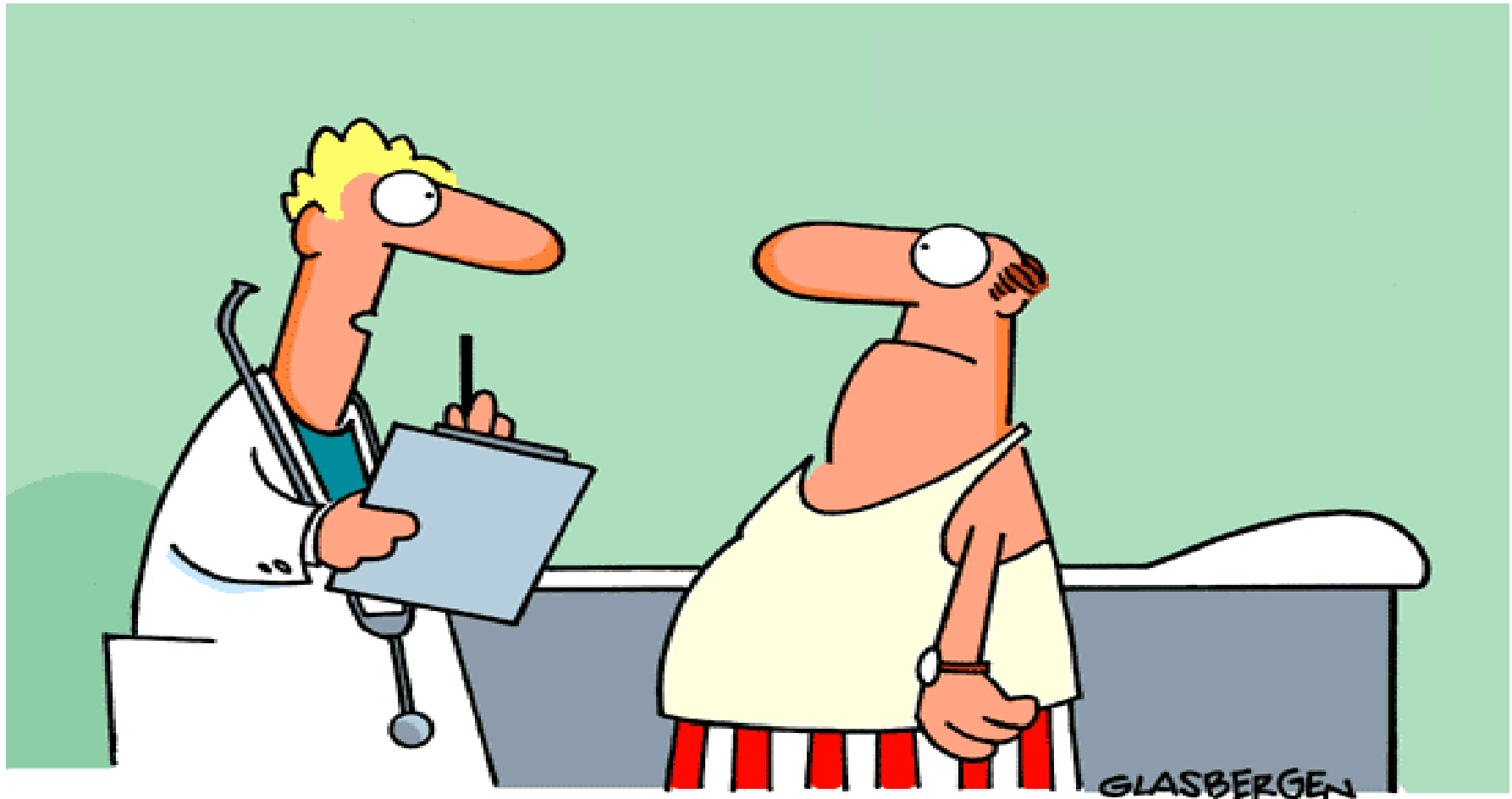
1. Minihane AM *et al. Arterioscler Thromb Vasc Biol.* 2000 Aug; 20(8):1990-7.
2. Masson LF *et al. Am J Clin Nutr.* 2003;77:1098-111.
3. Moreno JA *et al. J Nutr.* 2004;134:2517-2522.
4. a) Corella D *et al. Am J Clin Nutr.* 2001 Apr; 73(4):736-45 b) Marques-Vidal P *et al. Obes Res.* 2003 Oct;11(10):1200-6.  
 c) Mukamal KJ *et al. Atherosclerosis.* 2004 Mar;173(1):79-87 d) Bleich S *et al. J Neural Trans.* 2003 Apr;110(4):401-11.  
 e) Proc Nutri Soc 2004(65):5-10 f) Lussier-Cacan S *et al. Arterioscler Thromb Vasc Biol.* 2002 May 1:22(5):824-31.

# Apo E Genotype — Clinical Algorithm

	Apo E Affect on CVD Risk	Proposed Mechanism	Treatment	Response	Benefit
Apo E2 Genotype (2/2 ; 2/3)	Intermediate CVD Risk	Slow conversion of IDL to LDL leads to decrease in TC and increase in TG	Statin	↓ LDL	Beneficial
			Moderate Alcohol	↓ LDL / ↑ HDL	Beneficial
			Low Fat Diet	↑ small dense LDL % Limited ↓ LDL	Not Recommended
Apo E4 Genotype (3/4 ; 4/4)	Highest CVD Risk (42% increased risk of CVD)	Diminished HDL-binding leads to increase in LDL and TG; normal clearance process inhibited	Statin	Limited ↓ LDL	Limited
			Moderate Alcohol	↑ LDL / ↓ HDL	Not Recommended
			Low Fat Diet	↓ LDL / ↓ TG ↓ small dense LDL %	Beneficial

Song Y *et al. Ann Intern Med.* 2004 July 20;141(2):137-47

# Motivational Tactics for Exercise



**“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”**