Reversing Atherosclerosis: Part 1
Ateriology: Where Disease and Inflammation Collide

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Atherosclerosis continues to be the number one cause of death in the USA. Annually 1,000,000 people will suffer a heart attach; 1/3 of those will occur in people who have already suffered an event.

Current standard of care using risk factor identification and modification is inadequate to reduce the high rate of recidivism.

A new paradigm focusing on disease (atherosclerosis) is paramount; when disease is found the ‘root’ causes must be identified and treated.

Aggressively treating ‘root’ causes of atherosclerosis will dramatically reduce the risk of heart attacks and strokes and stop the high rate of recidivism.
Endothelial Shear Stress (ESS): Proportional to the Product of the Blood Viscosity ($\mu$) and Spatial Gradient of Blood Velocity at the wall ($dv/dy$)

$$ESS = \mu \frac{dv}{dy}$$

J Am Coll Cardio 2007;49:2379-2393
Pulsatile, Low and Oscillatory Endothelial Shear Stress (ESS)

J Am Coll Cardio 2007;49:2379-2393
Endothelial Sheer Stress (ESS) Profiling 3D Reconstructed LAD Artery

The Pascal (Pa) is the SI derived unit of pressure, internal pressure, stress, Young's modulus and tensile strength. It is a measure of force per unit area, defined as one newton per square meter.
Arterial Bifurcation: Substantial Retarding of the Flow on the Outer Wall
Low Endothelial Sheer Stress Promotes Atherosclerosis
Proposed Natural History of Coronary Atherosclerosis

J Am Coll Cardio 2007;49:2379-2393
## Different Heart Rates and Total Cardiac Beats Over Time

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart Rate 60 beats/minute</th>
<th>Heart Rate 80 beats/minute</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 min</td>
<td>3,600</td>
<td>4,800</td>
<td>1,200</td>
</tr>
<tr>
<td>24 hours</td>
<td>86,400</td>
<td>115,200</td>
<td>28,800</td>
</tr>
<tr>
<td>One year</td>
<td>31,536,000</td>
<td>42,048,000</td>
<td>10,512,000</td>
</tr>
<tr>
<td>10 years</td>
<td>315,360,000</td>
<td>420,480,000</td>
<td>105,120,000</td>
</tr>
</tbody>
</table>
Standard of Care
Addressing Modifiable Risk Factors
INTERHEART Study

- Hypertension
- Dyslipidemia
- Diabetes (Insulin resistance)
- Obesity-↑abdominal visceral fat “apple”
- FORK-consumption of fruits and vegetables
- FOOT-physical exercise
- Smoking
- Alcohol intake
- Psychosocial factors

Lancet 2004;364:937-952
Eat Slowly---Lose Weight---Feel Great!!

www.hapi.com
New Paradigm
Disease Based Platform

- Addressing traditional modifiable risk factors

  PLUS

- Genetics
- Periodontal testing
- Endothelial “Arteriology” assessment
- Inflammatory Biomarkers
- Other Biomarkers: NT-proBNP, Vitamin D
- Obstructive Sleep Apnea
What are you?

- **A lumenologist?**
  - Is the lumen open?
    - Stress testing
    - Angiography
    - Carotid Duplex Imaging
    - Ankle-Brachial Index

- **An arteriologist?**
  - Is disease present?
    - Carotid Intimal Media Thickness (cIMT)
    - Coronary Calcium Score
    - AAA for calcium
    - Femoral IMT
Lumenology

Traditional Cardiology

Is the lumen open?
Arteriology

Lumen 72%

New Paradigm

Is disease present?
REALITY: Most Heart Attacks are Caused by Non-Obstructing Plaque

Pre-MI Stenosis

- Yellow: >70%
- Light Blue: 50-70%
- Red: < 50%

200 Patients

- 14% >70%
- 18% 50-70%
- 68% < 50%

Stenosis severity by angiography of ASVD preceding MI

Circulation 1995;92:657-691
http://cvdrisk.nhlbi.nih.gov/calculator.asp

http://www.reynoldsriskscore.org
FRS and Reynolds Risk Score (RRS) Fails to Identify the Majority of Subjects Who Will Have an Event

http://www.reynoldsriskscore.org
http://my.americanheart.org/professional/Statements/Guidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
Disease Identification

Disease (+) events

Disease (-) events

No Disease
Personalizing Medical Care

• Effective medical management demands goal setting based, as much as possible, on the biological uniqueness of each patient
• Biological differences are grounded in genetics
• Genetics will drive the future of medicine
Genetics
Important “Root” Cause
You cannot get any more personal than your genetic makeup
Genetic Testing for EVERYONE
YES I am Talking about you!

- ApoE Genotype - Lifestyle advise
- KIF6 Genotype - Statin therapy
- 9p21 Genotype - Heart Attack Gene
- LPA [Lipoprotein(a)] Genotype - Aspirin treatment for primary CVD prevention
- ABO Blood Group - O lowest CVD risk
- Factor V Leiden - Coagulation disorder
- MyPerioID & MyPerioPath - Periodontal disease
Additional Genetic Testing
Optional

- CYP2C19*2*3-Plavix poor metabolizer
- CYP2CA9*17*-Plavix rapid metabolizer
- Prothrombin Mutation-coagulation disorder
- MTHFR677-folate metabolism
- MTHFR1298-folate metabolism
- LPA-Intron 25 Genotype-increased Lp(a)
- 4q25-AF Risk Genotype-Atrial fibrillation
- SLCO1B1 Genotype-Statin myopathy
## Apolipoprotein E Genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Apo E2 Response</th>
<th>Apo E3 Response</th>
<th>Apo E4 Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>Genotype</td>
<td>Genotype</td>
<td>Genotype</td>
</tr>
<tr>
<td>2/2</td>
<td>2/3</td>
<td>3/3</td>
<td>2/4</td>
</tr>
<tr>
<td>Population Frequency</td>
<td>1%</td>
<td>10%</td>
<td>62%</td>
</tr>
<tr>
<td>Fish Oil¹</td>
<td>↓↓TG ↓small dense LDL ↑HDL</td>
<td>↓TG ↓small dense LDL ↑HDL</td>
<td>↓TG ↓small dense LDL ↓HDL ↑↑LDL</td>
</tr>
<tr>
<td>Low Fat Diet²,³</td>
<td>↓LDL ↑small dense LDL</td>
<td>↓↓LDL ↔ small dense LDL</td>
<td>↓↓↓LDL ❤</td>
</tr>
<tr>
<td>Moderate Fat Diet³</td>
<td>↔LDL ↔ small dense LDL</td>
<td>↓LDL ↓small dense LDL</td>
<td>↓LDL 😞</td>
</tr>
<tr>
<td>Moderate Alcohol⁴</td>
<td>↑HDL ↓LDL</td>
<td>↑HDL</td>
<td>↓HDL ↑LDL 😞</td>
</tr>
</tbody>
</table>

*Chart represents a summary of reported metabolic responses seen with different Apo E genotypes*

Kinesin-like Protein 6 (KIF6)

- Kinesins: a family of motor proteins which transport organelles, protein complexes and mRNAs within a cell
- The genetic variant changes tryptophan to an arginine KIF6Trp719Arg
- This change results in a non-polar residue replacing a basic residue in the tail domain which may affect cargo binding or regulation in the motor domain

Science 2003;302:2130-2134
In CARE, carriers of the 719Arg risk allele received significant reduction of absolute risk for CVD events from pravastatin therapy. No significant reduction was observed in noncarriers.

In WOSCOPS, CVD risk reduction was significantly greater in carriers than in noncarriers.
PROVE IT TIMI 22

Carrier’s (+) BENEFIT

Non-Carrier’s (-) BENEFIT

J Am Coll Cardio 2008;51:449-455
Clinical Significance of KIF6 Testing

- **KIF6 Carrier**
  - May have higher lifetime cardiovascular risk
  - **ANY** statin is beneficial

- **KIF6 Non-carrier**
  - Still can be at risk; monitor for disease
  - When considering statin therapy choose simvastatin or rosuvastatin
NO Data that Atorvastatin Reduces Cardiovascular Disease in Women!

Risk Ratio

Hazard Ratio

Female  Male

All patients

Atorvastatin
Better

Placebo
Better

0.5 1.0 1.5

0.5 1.0 1.5

1.10 (0.57-2.12) 0.59 (0.44-0.77)

0.64 (0.50-0.83)

Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)  
Lancet 2003;361:1149-1158
9p21 Risk Variant Alters the Activity of ANRIL Resulting in Increased Risk of Atherosclerosis and Aneurysm
### 9p21 Polymorphism Carriers have Increased Risk of CVD and Aneurysm

<table>
<thead>
<tr>
<th></th>
<th>NON-CARRIER 27% population</th>
<th>9p21 CARRIER heterozygous 50% population</th>
<th>9p21 CARRIER homozygous 23% population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>myocardial infarction/cardiovascular disease</strong></td>
<td>no increased risk</td>
<td>up to 1.26X increased risk</td>
<td>up to 1.64X increased risk</td>
</tr>
<tr>
<td><strong>early myocardial infarction</strong></td>
<td>no increased risk</td>
<td>up to 1.49X increased risk</td>
<td>up to 2.02X increased risk</td>
</tr>
<tr>
<td>men &lt;50 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>women &lt;60 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>abdominal aortic aneurysm</strong></td>
<td>no increased risk</td>
<td>up to 1.36X increased risk</td>
<td>up to 1.74X increased risk</td>
</tr>
</tbody>
</table>
9p21 Genotype Reporting

Non-Carrier:
No Increased Risk

Heterozygous:
Increased Risk MI and AAA

Homozygous:
Increased Risk MI, AAA and Stroke
The Lipoprotein(a) [LPA] Gene
Lipoprotein(a)  
Lp(a)

- Apo(a) is a large glycoprotein comprised of loop-like repeating units called kringles (resembles a Danish pretzel)
- Apo(a) is linked by a disulfide bond to an LDL particle, producing a composite particle known as Lp(a)
- Lp(a) is potentially pro-thrombotic since it interferes with the action of plasminogen
- A variant in the LPA gene that substitutes a methionine residue for isoleucine at position 4399 (Ile4399Met) is associated with an increased risk for CVD
- Subjects with the LPA genetic variant also have a higher risk for thrombosis and therefore may derive more benefit from the anti-thrombotic properties of aspirin therapy
Women’s Health Study: LPA Variant & Aspirin RX Carriers Treated with ASA Ameliorated ↑ Risk

*NNT to prevent 1 major CVD event was 37 for carriers and 625 for noncarriers; ~15 times more bleeds for each CVD event prevented in noncarriers than in carriers

Circ Cardiovasc Genet 2011;4:565-573
Clinical Summary for LPA Genotyping

- Carriers of the LPA variant have higher Lp(a) levels and a ~2-fold higher risk of CVD; Hispanics 28%, Chinese and Japanese 16%; Caucasian 4%; African Americans 2%
- Women’s Health Study-carriers got good CVD, MI and ischemic stroke risk reduction with aspirin therapy: NNT 37
- Atherosclerosis Risk in Communities (ARIC) study-men and women carries had a decrease in CVD events with aspirin therapy
- Primary CVD Prevention and ASA: Based on this data, LPA genotyping should be assessed. CVD benefit of ASA in carriers outweighs the risk; ASA is not recommended in the noncarriers since the risk outweighs the benefit

ABO Blood Groups and CVD
Type ‘O’ Lower CVD Risk!

Arterioscler Thromb Vasc Biol 2012;32;2314-2320
Factor V Leiden

- Single point mutation in the F5 gene, G1691A arginine -> glutamine; named after the city Leiden (Netherlands), where it was 1st identified in 1994
- Most common inherited coagulation disorder in U.S. 5% Caucasians; 2% Hispanics; 1.2% African Americans; <0.5% Asian Americans
- Heterozygous = 3-8 fold increase risk of thrombosis
- Homozygous = 30-140 increase risk of thrombosis
- Overproduction of thrombin = excess fibrin formation -> excess clotting -> ↑ DVT and PE

Periodontal Testing: MyPerioID MyPerioPath

http://www.oraldna.com/tests.html
MyPerioID

Interlukin-1 and Periodontal Disease (PD)

• Interleukin-1 (IL-1) gene polymorphisms have been associated with increased levels of inflammatory mediators and several inflammatory diseases.
• IL-1 gene polymorphisms-IL1A (-889), IL1A (+4,845), and IL1B (+3,954), have been associated with chronic PD
• Any combination that includes the presence of a “T” at both IL-1A (+4845) and IL-1B (+3954) is defined as PST-positive and predisposes an individual to more severe PD which may require more aggressive treatment.

http://www.oraldna.com/tests.html

MyPerioPath
Periodontal disease (PD) and CVD

• A link between oral health and CVD has been proposed for more than a century.
• Possible links between PD and CVD has intensified since these two disorders share several common risk factors, including age, cigarette smoking and diabetes mellitus.
• Observational studies support an association between PD and CVD independent of known confounders.
• Although short-term periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction there is no evidence that they prevent CVD or modify its outcomes.

Arteriology = Inflammation

- **Endothelial “Arteriology” Assessment**
  - Carotid intima media thickness (cIMT)
  - Coronary calcium score (CCS)

- **Inflammation Assessment**
  - F$_2$-Isoprostanes (F$_2$-IsopS)
  - High-sensitivity C-reactive protein (hs-CRP)
  - Urine albumin/creatinine ratio (UACR)
  - Myeloperoxidase (MPO)
  - Lipoprotein-Associated Phospholipase A2 (Lp-PLA$_2$)
  - Fibrinogen

- **Other Biomarkers**: NT-proBNP, 25-OH Vitamin D
Carotid Intima Media Thickness (cIMT) is an Excellent Clinical Tool to Find and Monitor Plaque

- cIMT can detect subclinical atherosclerosis and an accelerated atherosclerotic process
- cIMT is an independent predictor of heart attack and stroke
- cIMT is noninvasive; inexpensive; repeatable without adverse effects
- cIMT can be used to monitor the atherosclerotic disease process
- cIMT adds prognostic power to conventional risk stratification tools (Framingham)

Circulation 2013;127:e6-e245
Plaque is defined as a cIMT of >1.2 mm in either the common, bifurcation or internal carotid artery.
Coronary Calcium Score (CCS)

- CCS documents presence of atherosclerosis
- Identifies patients at increased risk for cardiovascular disease and stroke
- Adds prognostic power to conventional risk stratification tools (Framingham)
- Alters therapeutic goal (lipids, BP, etc)
- Improve Compliance (Adherence)
- **CAVEAT:** Identifies patients who do not need further cardiac evaluation (zero CCS)

Circulation 2013;127:e6-e245
Coronary Artery Calcium (CAC) Score*

The calcium scale is a linear scale with 4 calcium score categories:

- \( \leq 10 \) none
- 11-99 mild
- 100-400 moderate
- >400 severe

*Calcium score correlates directly with risk of events and likelihood of obstructive CVD.
CAVEAT: Coronary Calcium Score ZERO
Inflammatory Biomarkers and the Progression of Atherosclerosis

-- $F_2$-Isoprostanes ($F_2$-IsoPs)
-- High-sensitivity C-reactive protein (hs-CRP)
-- Urine albumin/creatinine ratio (UACR)
-- Myeloperoxidase (MPO)
-- Lipoprotein-Associated Phospholipase A2 (Lp-PLA$_2$)
-- Fibrinogen
$F_2$-Isoprostanes

- 5-$F_2$-IsoP
- 8-$F_2$-IsoP
- 12-$F_2$-IsoP
- 15-$F_2$-IsoP
F$_2$-Isoprostanes are an Index of Oxidant Stress in Humans

- Oxidative reactions play a significant role in many biological conditions including chronic diseases such as atherosclerosis.
- F$_2$-isoprostanes are formed *in vivo* from the reaction of oxygen free radicals with arachidonic acid and have been found in oxidized LDL particles and atherosclerotic plaques.
- Risk factors for atherosclerosis like obesity, smoking and diabetes are associated with increased levels of F$_2$-isoprostanes in humans.
Increase in F₂-Isoprostanes Correlates with Body Mass Index

![Graph showing correlation between BMI and F₂-Isoprostanes levels. The graph indicates a significant increase in IsoP levels with higher BMI categories, with a p-value of less than 0.001.]
F₂-Isoprostane Formation is Markedly Increased In Cigarette Smokers and Abstinence Decreases Levels

hs-CRP
hs-CRP is NOT a Player

- Meta-analysis >80,000 subjects from genome-wide association study (GWAS); 18 SNP’s associated with CRP levels
- The more CRP-raising alleles the higher the mean CRP level, but this was NOT associated with an increased risk of CVD
- The analysis does not implicate CRP as a player in the atherosclerotic process. Rather, it seems to indicate that genetic predisposition to metabolic disorders such as insulin resistance (metabolic syndrome) or diabetes is linked to higher levels of CRP resulting in higher rates of CVD.

Circulation 2011;123:731-738
Metabolic Syndrome and hs-CRP
More Components Higher hs-CRP Level

C-reactive Protein (mg/L)

Number of Components of the Metabolic Syndrome

Circulation 2003;107:391-397
Albuminuria
So What is Albuminuria?

An elevated urinary albumin excretion is a marker of endothelial dysfunction that symbolizes the kidney’s way to translate the existence of vascular damage.
Albuminuria Predicts New Onset Diabetes in the General Population

New Onset Diabetes (%)

<table>
<thead>
<tr>
<th>Albuminuria (mg/day)</th>
<th>New Onset Diabetes (%)</th>
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</thead>
<tbody>
<tr>
<td>0 - 14</td>
<td>2.2</td>
</tr>
<tr>
<td>15 - 29</td>
<td>4.3</td>
</tr>
<tr>
<td>30 - 300</td>
<td>7.9</td>
</tr>
<tr>
<td>&gt;300</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Diabetes Care 2005;28:2525-2530
Albuminuria Linked to Insulin Resistance, Hypertension, LVD and CHF

Curr Opin Cardiol 2009;24:148-154
Definitions of “Albuminuria”

<table>
<thead>
<tr>
<th></th>
<th>Normo-albuminuria</th>
<th>Micro-albuminuria</th>
<th>Macro-albuminuria</th>
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</thead>
<tbody>
<tr>
<td>Urine albumin/creatinine ratio ‘UACR’ (mg/g creatinine)</td>
<td>&lt; 30</td>
<td>30 - 300</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

Diabetes Care 2004;27:S79-S83
Albuminuria Predicts Cardiovascular Risk at Levels BELOW Current Definition

Albuminuria Assessment in Patients with Hypertension and Diabetes Improves Cardiovascular Risk Stratification

LIFE Study: Composite Endpoint

Quintiles of Urine ACR (mg/g creatinine) among 1,063 Hypertension Patients with Diabetes

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Adjusted Hazard Ratio</th>
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<tr>
<td>&lt;6.9</td>
<td>1</td>
</tr>
<tr>
<td>6.9 – &lt;17.2</td>
<td>1.5</td>
</tr>
<tr>
<td>17.2 – &lt;45.0</td>
<td>2</td>
</tr>
<tr>
<td>45.0 – &lt;149.4</td>
<td>2.5</td>
</tr>
<tr>
<td>≥149.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Lancet 2002;359:995-1003
Urinary Albumin Excretion Predicts Cardiovascular Mortality in Type 2 Diabetes

Proportion CV Mortality

24.5%
2 log worse

10%
No Change

4.7%
2 log less

Am J Cardiol 2012;109:1743-1748
Urine Albumin Creatinine Ratio (UACR)* and CVD Risk

Risk when UACR > 7.5 in women and > 4.0 men

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hazard ratio</th>
<th>“p”</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>2.92</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*simple, inexpensive, independent predictor of CVD

Circulation 2005;112:969-975
Urine Albumin/Creatinine Ratio (UACR)

< 7.5 Women
< 4.0 Men
Myeloperoxidase (MPO)

MPO is elevated in 2 of every 50 patients
Myeloperoxidase (MPO)

- Member of the heme peroxidase family; store in granules in leukocytes; secreted during leukocyte activation; important in innate infectious disease host defense.

- Interacts with hydrogen peroxide and chloride to generate a powerful oxidant hypochlorous acid (HOCL) = BLEACH!!

- HOCL selectively targets tyrosine residues to generate chlortyrosine; HOCL also interacts with nitrogen species to generate nitrotyrosine.

- ApoA-I, the primary protein that makes up ~75% of HDL particles, is oxidized by chlortyrosine and nitrotyrosine at Trp72, and such oxidation impairs the cardioprotective functions of HDL

Nat Med 2014;18:193-203
Model of bidirectional conversion of HDL from anti-inflammatory (a) to proinflammatory (b)
Role of Myeloperoxidase and Mildly Oxidized LDL (Mox-LDL) in Triggering Inflammation and Atherosclerosis in Plaque Formation

Mediators of Inflammation 2013  
http://dx.doi.org/10.1155/2013/971579
Lipoprotein-Associated Phospholipase A2 (Lp-PLA$_2$)
Lp-PLA₂

- Lp-PLA₂ is association with lipoproteins, including LDL, HDL and to a lesser extent Lp(a); multiple inflammatory cells involved in atherogenesis secrete Lp-PLA₂, including monocytes, macrophages, neutrophils.
- Is a specific marker for vascular inflammation, i.e. rupture-prone plaque
- When elevated, Lp-PLA₂ confers a 2-fold risk for CVD and stroke events; identifies the “low risk person” who is actually at higher risk, mandating more aggressive lipid-lowering therapy
- Lp-PLA₂ is a PLAYER when it comes to atherosclerosis, not just a marker like CRP
Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY)

• This trial tested whether darapladib, a selective Lp-PLA$_2$ inhibitor, can safely lower the chances of having a heart attack or stroke in adults with chronic coronary heart disease.

• Enrollment: 15,828 patients

• RESULTS: The study did NOT meet the primary endpoint measure, which was time to first occurrence of any major adverse cardiovascular event.
NT-proBNP
Pro-BNP Derived Peptides: NT-proBNP and BNP

\[ t_{\frac{1}{2}} = 60-120 \text{ minutes} \quad \quad t_{\frac{1}{2}} = 18 \text{ minutes} \]
NT-proBNP Valuable Screening for Ventricular Dysfunction

- 1000 asymptomatic patients with type 2 DM or hypertension
- Levels >125 pg/mL identified echocardiography-defined moderate to severe ventricular dysfunction
- If level < 125 pg/mL, 98% probability there is no dysfunction
- Any patients with NT-proBNP >125 pg/mL warrants an echocardiogram;

J Cardiac Fail 2009;15:377-384
Happy Heart

NT-proBNP < 125 pg/ml
Potential Mechanisms for CVD Events with Vitamin D ↓

Relative Vitamin D Deficiency

Relative Hyperparathyroidism

Activation of RAAS

Depression?

HTN/LVH

Inflammation

DM/MetS

Atherosclerosis

CV Events

Pancreatic Beta Cell Dysfunction

Insulin Resistance

J Am Coll Cardiol 2011:58:1547-1556
Hypovitaminosis D is Associated with Insulin Resistance
25-Hydroxyvitamin D Level and the Risk of Mortality in the General Population

Curvilinear Relationship <20 and >50 ng/mL

Target Level 38-40 ng/mL

Arch Int Med 2008;168:1629-1637
Putative pathways for the physiological disturbances of intermittent hypoxia and sleep fragmentation to cause insulin resistance through activation of “classical” (white) or “lipotoxic” (grey) pathways

Physiol Rev 2010;90:47-112