Lessons Learned from Tim Russert: Investigating Residual Risk

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Tim Russert: Residual CV Risk?

- April 2008
  - Preclinical CAD at age 58, started on a statin
  - LDL-C 67mg/dL, Triglycerides 300mg/dL, HDL 32mg/dL
  - Performed well on stress test
- June 2008
  - AMI at work, attempts to resuscitate fail
- Too little, too late?

So, What’s New in Lipids since the ATP III Update in 2004?

- AHA endorsed LDL-C < 70 mg/dL as a reasonable target in secondary prevention
- Defining level for HDL-C as a risk is based on gender (< 40 men, < 50 women)
- Primary prevention with statin (JUPITER) is beneficial, especially in women and age > 70
- More data about CVD risk of MeS
- No data from statins in ESRD (dialysis), class 3/4 HF, dementia and aortic stenosis; some benefit in CKD
- Incremental benefit of fibrates combined with statin in high TG/low HDL subgroup (ACCORD Lipid) but no incremental benefit with niacin + statin (AIM HIGH)
**What will the NCEP ATP IV look like in 2011?**

More emphasis on the identification of primary CVD prevention patients for treatment? How to do this – biomarkers? Subclinical atherosclerosis?

- Do apo B, nonHDL-C and/or particle number become targets along with LDL-C?
- Incremental benefit with optimal statin treatment (to LDL-C goal):
  - Niacin (probably not)
  - Fenofibrate (low HDL/high TG)
  - Omega 3?
- What is the driver of incremental benefit?
  - HDL-C
  - Apo B or LDL-P
  - Both?
- Peri-procedural statins? Emphasis on Stage 3 and 4 CKD for risk reduction with statins?

**The Reality of ATP IV:**

No expert opinion
Evidence-based data only

- Determine risk level:
  - Highest (CHD, PAD, Stroke)
  - High risk primary prevention
- Highest risk:
  - Post ACS AT 80 mg (PROVE IT)
  - Stable CHD - SM 40 (HPS)
  - PRA 40 (LIPID, CARE)
  - AT 80 (TNT, IDEAL, SPARCL)

**The Reality of ATP IV:**

No expert opinion
Evidence-based data only

- High risk primary prevention:
  - PRA 40 (WOSCOPS)
  - SM 40 (HPS)
  - RSV 20 (JUPITER)
  - LOV 20-40 (AFCAPS/TexCAPS)
  - AT 10 (ASCOT LLA, CARDS)
JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56  P < 0.00001
Placebo 251 / 8901
Rosuvastatin 20 mg 142 / 8901

Number Needed to Treat (NNT5) = 25
- 44%

Incidence

JUPITER: Primary End Point in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects, events</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Participants</td>
<td>8901 (142)</td>
<td>1.25 (1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>3823 (65)</td>
<td>0.74 (0.62)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Placebo</td>
<td>5078 (77)</td>
<td>1.00 (1.00)</td>
<td>1.00</td>
</tr>
<tr>
<td>Racial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6356 (111)</td>
<td>1.25 (1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>2545 (31)</td>
<td>0.74 (0.62)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75</td>
<td>6210 (112)</td>
<td>1.25 (1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2791 (30)</td>
<td>0.74 (0.62)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3428 (59)</td>
<td>1.25 (1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Male</td>
<td>5473 (93)</td>
<td>0.74 (0.62)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>7908 (138)</td>
<td>1.25 (1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>1092 (18)</td>
<td>0.74 (0.62)</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

Primary and other composite end points as exploratory analysis of 5695 subjects > 70 yr in JUPITER
Time to Occurrence of MACE in JUPITER According to Achieved LDL-C

ASCOT LLA incidence of all-cause mortality and non-cardiovascular mortality over 11 year follow up

Residual Cardiovascular Risk in Placebo-Controlled Statin Trials
Residual Cardiovascular Disease Risk in Patients With Intensive Statin Therapy

CVD Events Across On-Treatment HDL-C Quintiles: Treating to New Targets (TNT) Study

Primary Endpoint Incidence Rates in JUPITER According to On-Treatment HDL-C and apoA-I Quartiles
Associations between HDL-C levels and cardiovascular outcomes: Statin treatment does not alter inverse relationship

Black circles indicate patients who are receiving statin interventions, and green circles indicate patients who are receiving a nonstatin control.

Figure: SCHEMATIC

Triglyceride Level Is Significant CVD Risk Factor: Meta-analysis of 29 Studies

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>CHD Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>210 years</td>
<td>5992</td>
<td></td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>4266</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7728</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1994</td>
<td></td>
</tr>
<tr>
<td>Fasting status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>7484</td>
<td></td>
</tr>
<tr>
<td>Nonfasting</td>
<td>2874</td>
<td></td>
</tr>
<tr>
<td>Adjusted for HDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4469</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5689</td>
<td></td>
</tr>
<tr>
<td>Overall CHD Risk Ratio*</td>
<td></td>
<td>1.72 (1.56-1.90)</td>
</tr>
</tbody>
</table>

*Participants in top vs bottom third of usual log-triglyceride values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (when). Adapted from Sarwar N, et al. Circulation. 2007;115(4):450-458.

What Is Non–HDL-C?

non-HDL-C = Total cholesterol – HDL-C

Diagram: Chart showing the components of non-HDL-C.
Elevated Triglycerides Are Metabolically Related to Small LDL and HDL Particles

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk

Elevated Triglycerides Are Associated With Increased Small LDL Particle Number
LDL-C, LDL-P and Apoprotein B in Metabolic Syndrome: Framingham Heart Study

Am J Cardiol 2008;102(suppl); 1K-34K

LDL-C 70-99 mg/dL (n=1484) 24% (n=364)

5th 20th 50th 80th percentile

43% (n=631) 21% (n=307) 11% (n=163)

Cromwell WC, Otvos JD. Am J Cardiol. 2006;98(12):1599-1602. Copyright © 2006 Elsevier Inc.

ADA/ACC 2008 Consensus Statement: Treatment Goals in Patients With Cardiometabolic Risk and Lipoprotein Abnormalities

<table>
<thead>
<tr>
<th>Goals</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-risk patient • Known CVD</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>• Diabetes plus 21 additional major CVD risk factors*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk patients • No diabetes or known CVD but 2 major CVD risk factors*</td>
<td>&lt;100 mg/dL</td>
<td>&lt;130 mg/dL</td>
<td>&lt;90 mg/dL</td>
</tr>
<tr>
<td>• Diabetes but no other major CVD risk factors*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In individuals on statin therapy who continue to have low HDL-C or elevated non-HDL-C, especially if CVD is present, treatment with a fibrate, niacin, or combination therapy is recommended. The preferred agent to use in combination with a statin is niacin...*  
*Major risk factors beyond diabetes include smoking, hypertension, and family history of premature CHD.*  
Effects of Statins on LDL-C and LDL-P

| Table 2: Effect of LDL-lowering therapy on LDL-C and LDL-P |
|-------------|---------------------|
| Treatment | LDL-C (mg/dL) | LDL-P (mg/dL) |
|             | In total | [%] | In total | [%] |
| Placebo    | 100      | 100   | 150      | 150   |
| Statin      | 100      | 100   | 150      | 150   |
| Statin + Ezetimibe | 100  | 100   | 150      | 150   |
| LDL-C (mg/dL) | In total | [%] | In total | [%] |
| Placebo    | 100      | 100   | 150      | 150   |
| Statin      | 100      | 100   | 150      | 150   |
| Statin + Ezetimibe | 100  | 100   | 150      | 150   |
| LDL-C (mg/dL) | In total | [%] | In total | [%] |
| Placebo    | 100      | 100   | 150      | 150   |
| Statin      | 100      | 100   | 150      | 150   |
| Statin + Ezetimibe | 100  | 100   | 150      | 150   |

Treatments that Alter Cholesterol Content of LDL

Change LDL-C and LDL-P Differentially

- **Cholesterol per particle decreases**
  - Statins
  - Statin + Ezetimibe or Bile Acid Sequestrates
  - Estrogen Replacement Therapy
  - Anti-retrovirals (some)
  - Low fat, High carb diet

- **Cholesterol per particle increases**
  - Fibrates
  - Niacin
  - Pioglitazone
  - Omega 3 FAs
  - Exercise
  - Mediterranean and low carb diet
  - Therapy

- **Less Change in Cholesterol per Particle with**
  - Bile Acid Sequestrate or Ezetimibe Monotherapy

- **Similar Change in LDL-C and LDL-P**


What is the Evidence that adding a drug to statins can provide incremental outcomes benefit?
**ACCORD: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean or %</th>
<th>Characteristic</th>
<th>Mean or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62</td>
<td>Total Cholesterol (mg/dl)</td>
<td>175</td>
</tr>
<tr>
<td>Women %</td>
<td>31</td>
<td>LDL-C (mg/dl)</td>
<td>101</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
<td>HDL-C (mg/dl)</td>
<td>38</td>
</tr>
<tr>
<td>White %</td>
<td>68</td>
<td>Triglyceride (mg/dl)*</td>
<td>162</td>
</tr>
<tr>
<td>Black %</td>
<td>15</td>
<td>Blood pressure (mm Hg)</td>
<td>134/74</td>
</tr>
<tr>
<td>Hispanic %</td>
<td>7</td>
<td>Serum creatinine (mg/dl)</td>
<td>0.9</td>
</tr>
<tr>
<td>Secondary prevent %</td>
<td>37</td>
<td>Current smoking %</td>
<td>15</td>
</tr>
<tr>
<td>DM duration (yrs)*</td>
<td>9</td>
<td>On a statin %</td>
<td>60</td>
</tr>
<tr>
<td>A1c (%)*</td>
<td>8.3</td>
<td>On another LLA %</td>
<td>8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32</td>
<td>On Insulin %</td>
<td>33</td>
</tr>
</tbody>
</table>

*Median values

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**ACCORD Outcomes**

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**ACCORD: Primary Outcome By Treatment Group and Baseline Subgroups**

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Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high triglycerides: Impact on Global Health (AIM HIGH) Results

- 3414 subjects with CVD; age 64; 34% with T2DM and 71% with MeS; 94% had prior statin use
- Randomized to simvastatin to reduce LDL-C < 80 mg/dL, and then to niacin ER 2 gm in 1718 or PBO in 1696
- Baseline lipids:
  - LDL-C 71
  - TG 161
  - HDL 35
  - nonHDL-C 186
  - apo B 81

AIM HIGH: HDL-C at Baseline & Follow-up

 AIM HIGH: LDL-C at Baseline & Follow-up
AIM HIGH: Primary Outcome

![Graph showing cumulative % with primary outcome over time for combination therapy and monotherapy.](image)

**Primary Outcome**

- **HR 1.02, 95% CI 0.87, 1.21**
- Log-rank P value = 0.79

**N at risk**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>1696</td>
<td>1581</td>
<td>1381</td>
<td>910</td>
<td>436</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>1718</td>
<td>1696</td>
<td>1366</td>
<td>903</td>
<td>428</td>
</tr>
</tbody>
</table>

Trials with Niacin and Statin Combination

<table>
<thead>
<tr>
<th>Trial</th>
<th>Therapy</th>
<th>End Point</th>
<th>N Patients</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM-HIGH</td>
<td>Simvastatin + Niacin ER</td>
<td>CVD</td>
<td>3414</td>
<td>2nd prevention</td>
</tr>
<tr>
<td>HPS 2-THRIVE</td>
<td>Simvastatin + Niacin ER + laropiprant</td>
<td>CVD</td>
<td>25 000</td>
<td>7000 DM</td>
</tr>
</tbody>
</table>

1. [http://www.aimhigh-heart.com](http://www.aimhigh-heart.com)
2. [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)


So, What did the EAS/ESC do with their guidelines in 2011?
ESC/EAS Guidelines for Managing Dyslipidemia

• Risk based approach (risk factors and SCORE)
  A. Very high risk:
   - Documented CVD (invasive and noninvasive) – MI, stroke, CABG, ACS, PAD, carotid plaque
   - Type 2 DM (CHD, CKD)
   - Type 1 DM with microalbumin, end organ damage
   - CKD
   - SCORE ≥ 10% 10 yr risk for fatal CVD (3 X higher for fatal and nonfatal events)
  B. High risk:
   - A. markedly elevated single RF (severe HTN, HeFH)
   - B. Type DM at any age
   - C. SCORE 2 5 and < 10%
  C. Moderate risk:
   - SCORE 1 to < 5%; risk can be modified by FHx, HDL-C, Lp(a), apo B and MeS

Atherosclerosis 2011: 217: S1-S44
Eur Heart J 2011: 32:1769-1818

ESC/EAS Guidelines for Managing Dyslipidemia

• Lipid targets:
  Primary - LDL-C
  NonHDL-C and apo B as alternative targets in mixed dyslipidemia, T2 DM, MeS, CKD
  No targets for HDL-C and TG
  Lp(a) in premature CHD or FHx of premature CHD
  Very high risk:
  - LDL-C < 70 mg/dL (< 1.8 mmol/L) or ≥ 50% reduction from baseline: apo B < 80 mg/dL, nonHDL-C < 100 mg/dL
  High risk:
  - LDL-C < 100 mg/dL (< 2.5 mmol/L), apo B < 100 mg/dL, nonHDL-C < 130 mg/dL
  Moderate risk:
  - LDL-C < 115 mg/dL (< 3 mmol/L)

Atherosclerosis 2011: 217: S1-S44
Eur Heart J 2011: 32:1769-1818

ESC/EAS Guidelines for Managing Dyslipidemias

• Tests not recommended for routine use:
  Lipoprotein particle size
  Lp(a), except in premature CHD or FHx
  Genotyping
  hs-CRP as a target of treatment
• Special populations:
  1. Autoimmune chronic inflammatory conditions (RA, SLE, psoriasis) are at high risk
  2. Genetic dyslipidemias: FCHL (1:100) => apo B > 120 mg/dL + TG > 135 mg/dL;
  HeFH (1:500)
  3. PCI: load with high dose statin before procedure
  4. Elderly (> 70 yr): consider for primary prevention
Summary

• CTTC meta-analysis confirms an approx 20% reduction in MACE and 10% reduction in total mortality for 1 mmol/L ↓ in LDL-C, with no lower limit.
• Residual CVD risk remains after treatment with statins (including intensive statin therapy) to reduce LDL-C.
• Low HDL-C probably contributes to residual risk for CVD, even if LDL-C is at goal.
• Elevated triglycerides are a marker for increased remnant lipoproteins that can be atherogenic as well as for increased particle numbers, especially in individuals with insulin resistance.
• Non–HDL-C captures these remnant particles and is a better predictor of CVD risk than LDL-C, and is equal to apo B.

Summary (Continued)

• After LDL-C, guidelines recommend targeting non–HDL-C (possibly Apo B) to optimize risk reduction and suggest niacin, fibrates and/or intestinally-acting drugs (colesevelam, ezetimibe) added to statins.
• Identification of appropriate primary prevention candidates for statin Rx is important because therapy will benefit women and age > 70.