PRESS RELEASE

New Insights Link Low HDL-Cholesterol and Elevated Triglycerides with Coronary Heart Disease and Microvascular Complications in Patients at Goal for LDL-Cholesterol

Surveys establish residual vascular risk is associated with atherogenic dyslipidemia suggesting the need to reconsider approach to management of lipids

Residual Risk Reduction initiative (R³i) Foundation presents early findings from unique global investigation into effects on residual macrovascular and microvascular risk

1st September 2009 – Barcelona, Spain – Low levels of high-density lipoprotein cholesterol (HDL-C) and raised triglycerides, affecting millions of patients worldwide, are strongly linked to significantly increased risk of coronary heart disease (CHD) even in patients who achieve or surpass current low density lipoprotein cholesterol (LDL-C) targets.

This has been demonstrated in new analyses of the landmark Prospective Cardiovascular Münster (PROCAM) and the REsiduAl risk Lipids and Standard Therapies (REALIST) surveys, the latter funded and conducted by the Residual Risk Reduction Initiative Foundation or R³i. These data have been presented today at the European Society of Cardiology (ESC) congress.

The final objective of the R³i is to significantly reduce the incidence of both major macrovascular events and microvascular complications (e.g. of type 2 diabetes or affected by the metabolic syndrome) beyond what is already achieved with current treatments.¹,²

Earlier studies, largely conducted in patients treated with statins show that lowering LDL-C to currently recognized goals only reduces the relative risk of macrovascular disease by about 23 percent.³

“The residual vascular risk driven by the increasing epidemic of obesity, metabolic syndrome and type 2 diabetes is not being adequately treated by clinicians,” stated Professor Frank Sacks from Harvard Medical School, Boston, USA and Vice-president of R³i. “While LDL-C is appropriately the current target, we have taken LDL-C reduction to its therapeutic limits without abolishing CVD events. Therefore we urgently need new strategies to address other modifiable risk factors such as atherogenic dyslipidemia.”
New insights into lipid-related macrovascular risk

Professor Gerd Assmann, member of the R³i International Steering Committee and President of the Board of the Assmann-Foundation for Prevention, presented a new analysis from PROCAM in which 823 men who survived a myocardial infarction (MI) were matched with an equal number of controls free from MI. This analysis, which was funded by the R³i, demonstrated:

- Low HDL-C and/or elevated triglycerides (TG) was seen in nearly two-thirds of MI patients
- When all risks factors were matched, the odds of experiencing a MI were increased five-fold for men with LDL-C at target (≤100mg/dL) presenting a low level of HDL-C (<45 mg/dL) and an elevated level of TG (>150 mg/dL)

The initial macrovascular findings of REALIST were also presented by Professor Frank Sacks, Vice-President of the R³i. This case-control study conducted in 170 patients hospitalized with CHD in Boston, USA, at goal for LDL-C, matched with 175 controls free from CHD shows that:

- High TG and low HDL-C are strong indicators of residual risk of CHD
- High TG and low HDL-C levels each contribute to the risk of a coronary event in patients with LDL-C levels ≤130 mg/dL or even LDL-C ≤70 mg/dL
- TG and HDL-C appear to act synergistically with the impact of TG increasing when HDL-C is low and the impact of HDL-C increasing when TG levels are high
- When moving from the lowest levels of TG and highest levels of HDL-C to the highest levels of TG and lowest levels of HDL-C, the risk of CHD increases 10-fold

Addressing atherogenic dyslipidemia may reduce the microvascular complications of type 2 diabetes

REALIST is also evaluating the risk of microvascular complications in patients with type 2 diabetes who achieve or approach LDL-C goal. Data collected by Professor Michel Hermans from the Cliniques Universitaires Saint-Luc in Brussels, Belgium, were presented by Professor Paola Fioretto, from the Department of Medical and Surgical Sciences, University of Padua, Italy and showed that:

- Low HDL-C, elevated TG and elevated non-HDL-C levels were more prevalent in patients who developed microvascular complications
• High TG levels are associated with increased risk of incident retinopathy, blindness and diabetic kidney disease

• Low HDL-C levels are associated with incident diabetic kidney disease

Similar to the findings of the macrovascular REALIST survey, the initial microvascular data showed that patients with incident microvascular complications of type 2 diabetes are more likely to present with atherogenic dyslipidemia even when LDL-C is nearly at goal (≤ 130mg/dL).

“Further analysis of microvascular data from this and other centers should confirm the relationship between atherogenic dyslipidemia and microvascular complications of type 2 diabetes,” said Professor Fioretto.

Implications of the R³i research program for future treatment

The REALIST research program is being globally extended and data are currently being collected in 27 centers in 12 countries around the world. This will support the major global program of research, education and advocacy being implemented by the R³i.

The ultimate objective of the R³i Foundation is to identify new indicators of macro- and microvascular residual risk as targets for future treatment strategies.

Residual vascular risk – A public health emergency

“Further reduction of LDL-C by use of the maximum permissible statin dosage is unlikely to be able to substantially lower this residual, largely non-LDL-C mediated risk,” says Professor Gerd Assmann from the University of Münster, Germany.
Therefore, while statins are effective, other treatment strategies are urgently needed to address the residual vascular risk which persists in patients despite current standards of care. While the R³i research program will help define appropriate targets for intervention in patients who remain at high residual vascular risk, the ongoing outcomes trials such as ACCORD, AIM-HIGH and HPS2-THRIVE will help determine new treatment strategies to address this risk.

“The R³i has a huge task ahead to get people recognizing the threat of residual vascular risk and acting to better manage it,” said Professor Jean-Charles Fruchart of the University of Lille, France and President of the R³i. “We have to look beyond using statins as a silver bullet to reduce LDL-cholesterol. The mindset that reducing one component to prevent heart disease is wrong and needs to change.”

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Notes to Editors

More information on the R³i is available from:
The R³i website: www.r3i.org

Epidemiological study methods

The PROCAM analysis used a case-control approach in which 823 men who had survived a MI were matched with an equal number of controls. Patients, who were matched for age, smoking status, type 2 diabetes status, blood pressure and LDL-C to an equal number of MI-free controls from the PROCAM cohort of 50,000 participants, a unique prospective investigation of coronary artery disease (CAD) and stroke risk factors in Germany.

The macrovascular REALIST survey was designed to determine, in patients at goal for LDL-C (≤ 130 mg/dL whether treated or untreated for elevated LDL-C) with a first or subsequent coronary event, whether low HDL-C and/or elevated TG levels are associated with a significant risk of coronary event after adjustment for other risk factors. Adult male or female patients admitted to coronary care units (CCUs) or explored in cardiac catheter laboratories were matched with controls hospitalized for other reasons.
The microvascular REALIST survey was designed to determine whether low HDL-C and/or elevated TG levels are associated with a significant residual risk of microvascular complications. Data will be adjusted for other risk factors such as age, sex, diabetes status, LDL-C levels, HbA1c, blood pressure, BMI and smoking in patients with type 2 diabetes nearly at goal for LDL-C and presenting with incident microvascular complication (retinopathy, maculopathy or nephropathy). Diabetic neuropathy is an exploratory disease due to difficulties in establishing it with certainty in retrospective analysis. The REALIST surveys are currently being conducted in Belgium, Croatia, France, Italy, Japan, Philippines, Poland, Saudi Arabia, Spain, Thailand, Turkey and the U.S.

**What is residual vascular risk?**

Residual vascular risk is defined as the significant residual risk of macrovascular events and microvascular complications which persists in most patients despite current standards of care including achievement of low-density lipoprotein (LDL-C) goal and intensive control of blood pressure and blood glucose.

Although statin therapy is the cornerstone of dyslipidemia management, LDL-C lowering with statins reduces the risk of major coronary events by approximately one-quarter, with 77 percent of the relative risk of events still occurring.\(^3\)

Multifactorial intensive therapy (including statins) is insufficient to prevent the development or progression of microvascular disease (retinopathy, nephropathy, neuropathy) in up to 50 percent of patients with type 2 diabetes.\(^8\)

**Atherogenic Dyslipidemia and Residual Vascular Risk**

Atherogenic dyslipidemia is characterized by elevated TG and low levels of HDL-C.

In the past three decades in the U.S., while the prevalence of abnormal levels of LDL-C has decreased, the prevalence of combined abnormal TG (\(\geq 150\) mg/dL) and HDL-C (\(< 40\) mg/dL) has doubled and the prevalence of elevated TG (\(\geq 150\) mg/dL) has increased five-fold.\(^9\) Elevated TG (\(> 150\) mg/dL) is also common, affecting about 50 percent of adults with prior CVD.\(^10\)

Atherogenic dyslipidemia contributes to the increased risk of macrovascular events such as myocardial infarction and stroke, and may be implicated in microvascular complications such as diabetic eye, kidney and lower limb disease.\(^{11}\)
• Among patients achieving LDL-C <70 mg/dL with a statin, CVD risk is almost 60 percent greater for patients with TG >200 mg/dL.12

• In patients achieving LDL-C <70 mg/dL with a statin, CV risk was higher in patients with a low HDL-C (HDL-C <37 mg/dL vs. those with a HDL-C >55 mg/dL)13

The mission of R³i

To reduce the significant residual risk of macrovascular events and microvascular complications which persists in most patients despite current standards of care including achievement of low density lipoprotein goal and intensive control of blood pressure and blood glucose.

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References:


