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Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Describe the effects of different dyslipidemia phenotypes from childhood to adulthood and their interaction with nonlipid cardiovascular risk factors and the metabolic syndrome on markers of subclinical atherosclerosis
- Compare the usefulness of the triglyceride/high-density lipoprotein (HDL) ratio versus total cholesterol/HDL ratio in predicting insulin resistance and cardiometabolic risk
- Examine the efficacy and safety of single-pill atorvastatin/ezetimibe therapy for the simultaneous treatment of hypertension and dyslipidemia among African American patients who are at risk for cardiovascular disease

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Off-Label Disclosure

Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Such uses will be noted at the end of the article.

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CLINICAL INSIGHTS® IN

LIPID Management

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Effects of Dyslipidemias From Childhood to Adulthood on CIMT, Elasticity, and Brachial Flow-Mediated Dilatation: The Cardiovascular Risk in Young Finns Study

Atherosclerosis begins in early life, especially in children and adolescents with high levels of low-density lipoprotein cholesterol (LDL-C). Dyslipidemias, the major cause for atherosclerosis, are suggested to act synergistically with nonlipid risk factors and the components of the metabolic syndrome (MetSyn) to increase atherogenesis. Juonala and colleagues conducted the present study to examine the effects of different dyslipidemia phenotypes from childhood to adulthood and their interaction with nonlipid cardiovascular risk factors and MetSyn on the risk of subclinical atherosclerosis.

Children and adolescents (aged 3 to 18 years; n=2,265) from the Cardiovascular Risk in Young Finns Study, which started in 1980, participated in this study. Phenotyping of type IIa, IIb, and IV dyslipidemias, and hypohigh-density lipoprotein (HDL) cholesterolemia was performed using longitudinal data on lipid values during several follow-up studies between 1980 and 2001. Subjects with high concentrations of LDL-C or triglycerides (TG) had type IIa or IV dyslipidemia, while subjects with increased levels of both LDL-C and TG had type IIb. The 21-year follow-up was conducted in five centers between 2001 and 2002. The authors assessed the associations of different dyslipidemia phenotypes with markers of subclinical atherosclerosis, carotid intima-media thickness (CIMT), elasticity, and brachial flow-mediated dilatation (FMD) among these subjects.

Compared with controls, patients with type IIb dyslipidemia had significantly increased

CIMT ($P<0.01$). This difference remained significant when adjusted for sex, age, and other risk factors ($P<0.03$). In addition, they were estimated to have 0.043-mm thicker CIMTs than controls. Moreover, CIMT was shown to increase significantly more with the number of major nonlipid risk factors (smoking, elevated blood pressure [BP], diabetes, and positive history of coronary heart disease) ($P<0.001$) or with presence of MetSyn ($P<0.05$).

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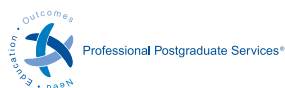
Carotid elasticity decreased in patients with types IIb or IV dyslipidemia ($P<0.05$). However, these differences became nonsignificant ($P>0.30$) when adjusted for BP. No differences in brachial FMD were observed between subjects with or without dyslipidemia.

Juonala and associates concluded that type IIb dyslipidemia increases CIMT in young adults, with deleterious effects beginning in childhood/adolescence. Further, individuals with type IIb dyslipidemia are more vulnerable to the effects of nonlipid, cardiovascular risk factors and MetSyn. The authors also suggest that identification of young subjects with increased levels of these risk factors and MetSyn is important to prevent cardiovascular disease in adults.

Juonala M, Viikari JS, Ronnema T, et al. Associations of dyslipidemias from childhood to adulthood with carotid intima-media thickness, elasticity, and brachial flow-mediated dilatation in adulthood. The Cardiovascular Risk in Young Finns Study. *Arterioscler Thromb Vasc Biol*. 2008 Feb 28; [Epub ahead of print].

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^b Dr Chen is a medical writer at Professional Postgraduate Services®. She has indicated no relevant financial relationships.



Post-Test Question 1

Based on the findings of this study, which phenotype of dyslipidemias caused a significant increase in CIMT in young persons?

- a. Type IIa
- b. Type IIb
- c. Type IV
- d. hypoHDL-cholesterolemia

Commentary

John C. LaRosa, MD, President of SUNY Downstate Medical Center, Brooklyn, New York. Education Council Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™).

This article represents the latest in a series of papers from the Cardiovascular Risk in Young Finns Study, a prospective, observational study that started in 1980 and included 2,265 patients (aged 3–18 years). Patients were grouped into five categories (normal, type IIa, type IIb, type IV, and hypohigh-density lipoprotein [HDL]-cholesterolemia) by an average of four measurements of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides (TG) measured in 1980, 1983, 1986, and 2001.

In 2001, carotid intima-media thickness (CIMT), carotid diameter and elasticity (compliance), and brachial flow-mediated diameter measurements were correlated with the average of the four separate lipid levels measured between 1980 and 2001. Significant correlations between type IIb hyperlipoproteinemia (HLP) and CIMT and elasticity, and type IV HLP and carotid elasticity were demonstrated. This study confirms the importance of LDL-C and TG concentrations in predicting carotid thickening and nonelasticity. The lack of concurrent longitudinal measures of vascular parameters, however, precludes any conclusions about correlations between changes in lipid parameters and those in carotid anatomy and function.

The TG/HDL Ratio Versus TC/HDL Ratio for Predicting Insulin Resistance and Cardiometabolic Risk in the Framingham Offspring Cohort

Increased triglycerides (TG) and decreased high-density lipoprotein cholesterol (HDL-C) are considered key risk factors for the development of insulin resistance (IR). Although the TG/HDL-C ratio has been used in recent studies as a clinical indicator for IR, results were inconsistent. The total cholesterol (TC)/HDL-C ratio is also widely used to assess lipid atherogenesis. However, the utility of this ratio for predicting IR or coronary heart disease (CHD) risk is not clear. In the present study, Kannel and colleagues compared the usefulness of these lipid ratios in predicting IR and CHD risk.

This study enrolled subjects who attended the examination cycle 5 (1991–1995) of the Framingham Offspring Study (n=3,014; mean age 54 years; 55% women). Logistic regression was used to construct receiver-operator characteristic curves for predicting age- and gender-adjusted prevalence of IR, with lipid ratios as predictors. Multivariable Cox regression was used to evaluate whether adjusting for lipid ratios would attenuate the association of IR with CHD.

Cross-sectional analyses of age- and gender-adjusted correlations of IR with multiple lipid measures, including their ratios, indicated a highly significant and fairly strong relation of IR with TG/HDL-C (0.46) and TC/HDL-C (0.38) ratios.

The performance of the TG/HDL-C ratio for predicting IR, evaluated by the area under the receiver-operator characteristic curves, was shown to be fair (0.745; 95% confidence interval [CI]; 0.726–0.764) and only slightly higher than that of the TC/HDL-C ratio (0.707; 95% CI; 0.687–0.727; $P < 0.001$ for comparison).

On follow-up (mean 6.4 years), 112 patients experienced a first CHD event. IR was strongly associated with marked increases in CHD risk, with an adjusted hazard ratio of 2.71 (95% CI; 1.79–4.11). The impact of IR on CHD risk remained significant after adjustment for lipid ratios; moderate decreases were observed when adjusted for TG/HDL-C (16.6%) or TC/HDL-C (14.4%) ratios.

The authors concluded that the TG/HDL-C ratio was the best predictor among those evaluated for IR and its associated cardiometabolic risk. However, the performance of this ratio in predicting IR is only slightly better than that of the TC/HDL-C ratio.

Kannel WB, Vasan RS, Keyes MJ, et al. Usefulness of the triglyceride–high-density lipoprotein versus the cholesterol–high-density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). *Am J Cardiol*. 2008;101(4):497-501.

Post-Test Question 2

Based on findings from an evaluation of patients from the Framingham Offspring Study, which lipid variable best predicts IR and cardiometabolic risk?

- TC/LDL-C
- TG/LDL-C
- TG/HDL-C
- LDL-C/HDL-C

Single-Pill Amlodipine/Atorvastatin Therapy Effectively Attained Cholesterol and Blood Pressure Goals in African Americans: The CAPABLE Trial

African Americans have a greater risk of stroke and a higher prevalence of hypertension (HTN), compared with Caucasians. Only 6.5% of African Americans with concomitant HTN and dyslipidemia achieve their goals for low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) versus 9.0% of the overall US population. Flack and colleagues conducted the Clinical Utility of Caduet in Simultaneously Achieving Blood Pressure and Lipid End Points (CAPABLE) trial to examine the efficacy and safety of single-pill amlodipine/atorvastatin therapy for the simultaneous treatment of hypertension (HTN) and dyslipidemia as an initial treatment or in combination with other antihypertensive drugs, among African Americans.

The CAPABLE trial was a 20-week, office-based, open-label, noncomparative, multicenter trial including patients with concomitant uncontrolled HTN and dyslipidemia (treated or untreated). Patients were assigned to three cardiovascular (CV) risk groups based on criteria outlined in The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines: no additional risk factors (group 1), ≥ 1 CV risk factor (group 2), or coronary heart disease (CHD) or CHD risk equivalent (group 3). Eight different dosages of single-pill amlodipine/atorvastatin were flexibly titrated. The primary efficacy assessment was the percentage of intention-to-treat (ITT)

patients who achieved both their JNC 7 BP and NCEP ATP III LDL-C goals at endpoint.

Of the 1,170 African American patients screened, 499 received drug therapy. At endpoint, 236 of 489 patients (48.3%) achieved both BP and LDL-C goals (vs 4 of 484 [0.8%] at baseline). Dual goal attainment was higher in CV risk groups 1 and 2 than in group 3, and was slightly lower (43.6%) in patients with uncontrolled LDL-C at baseline. The BP goal was attained by 280 of 493 patients (56.8%) at endpoint (vs 7 of 494 [1.4%] at baseline), and the LDL-C goal was achieved by 361 of 490 patients (73.7%) in the ITT population (vs 138 of 484 [28.5%] at baseline). Titration analyses indicated an apparent reluctance to titrate to higher doses, especially for the statin component. Among the 499 patients receiving drug therapy, the most common treatment-related adverse events were peripheral edema (17 patients [3.4%]), headache (11 [2.2%]), myalgia (11 [2.2%]), and constipation (10 [2.0%]).

Based on these observations, the authors concluded that single-pill amlodipine/atorvastatin therapy was well tolerated and effectively improved both HTN and dyslipidemia in African Americans who were at risk for CV disease.

Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. *Mayo Clin Proc.* 2008;83(1):35-45.

Post-Test Question 3

Based on the findings in CAPABLE, what percentage of patients who received single-pill amlodipine/atorvastatin therapy attained both BP and LDL-C goals at endpoint?

- 50%
- 75%
- 25%
- 10%