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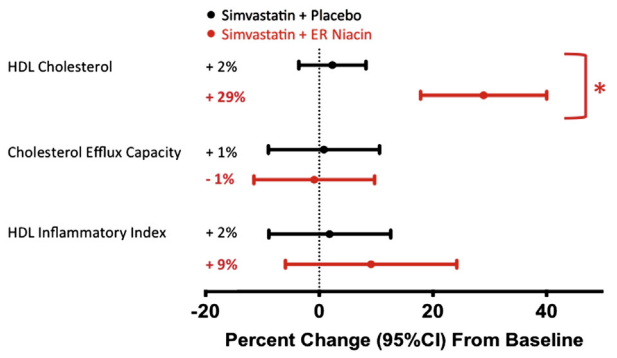

Figure 1 Effect of Niacin on HDL-C Levels and Metrics of Functionality

Mean percent change from baseline for each treatment group is depicted for high-density lipoprotein cholesterol (HDL-C) levels, cholesterol efflux capacity, and HDL inflammatory index. *Indicates p value of < 0.05 for change compared with placebo. CI = confidence interval; ER = extended release.

coefficient of variation was 5.5% for cholesterol efflux capacity and 4.3% for HDL inflammatory index.

Bivariate correlation analysis demonstrated a moderate association ($r = 0.56$; $p = 0.002$) between HDL-C levels and cholesterol efflux capacity. However, no significant association was noted between HDL inflammatory index and either HDL-C levels ($r = 0.18$) or cholesterol efflux capacity ($r = -0.16$). Only the HDL inflammatory index was associated with log-transformed values of C-reactive protein ($r = 0.37$; $p = 0.02$).

The impact of the 2 treatment regimens on HDL-C levels and functional metrics are displayed in Figure 1. As expected, the addition of niacin therapy led to a robust increase in average HDL-C from 46 to 57 mg/dl ($p = 0.001$ compared with baseline; $p = 0.001$ compared with placebo). However, no change was noted in either cholesterol efflux capacity (mean change −1%; 95% confidence interval: −11% to 10%) or HDL inflammatory index (mean change 9%; 95% confidence interval: −6% to 24%).

These results thus indicate the feasibility of using 2 complementary assays of HDL function in a small drug study. The addition of niacin to statin therapy led to favorable changes in patients' lipid profiles without a demonstrable effect on HDL functionality, thus providing one potential mechanistic hypothesis for the disappointing results in recent clinical trials.

The strengths of this study include its randomized, placebo-controlled, prospective design and the use of robust assays with previous relationship to cardiovascular disease phenotypes. Limitations include small size, although the matched-pairs statistical plan afforded 80% power to detect a 13% and 15% improvement in cholesterol efflux capacity and HDL inflammatory index, respectively. Furthermore, any potentially beneficial effect of niacin via LDL-C or lipoprotein(a) reduction would not have been detected owing to the HDL specificity of the assays. (Carotid Atherosclerosis Regression at Magnetic Resonance Assessment; NCT00307307).

*Amit V. Khera, MD†
Parin J. Patel, MD‡
Muredach P. Reilly, MD‡
Daniel J. Rader, MD‡

*Department of Medicine
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115
E-mail: avkhera@partners.org

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From the †Department of Medicine, Brigham & Women's Hospital, Boston, Massachusetts; and the ‡Division of Translational Medicine and Human Genetics, Department of Medicine, Cardiovascular Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

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REFERENCES

1. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–67.
2. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med 2011;364:127–35.
3. Li XM, Tang WH, Mosior MK, et al. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. Arterioscler Thromb Vasc Biol 2013;33:1696–705.
4. Patel PJ, Khera AV, Jafri K, et al. The anti-oxidative capacity of high-density lipoprotein is reduced in acute coronary syndrome but not in stable coronary artery disease. J Am Coll Cardiol 2011;20:2068–75.
5. Airan-Javia SL, Wolf RL, Wolfe ML, et al. Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low- and high-dose simvastatin monotherapy. Am Heart J 2009;157:687.e1–8.

Letters to the Editor

Pregnancy in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

We read with interest the paper by Marcus et al. (1) published in the May 14, 2013 issue of the *Journal*. The authors brought to light the complex nature of clinical genetics in arrhythmogenic right ventricular cardiomyopathy (ARVC) patients. Overall, this paper provides an important review of the current state of clinical genetic testing for this rare condition. We applaud the authors for their confirmation of the Heart Rhythm Society/European Heart Rhythm Association guidelines (2) in recommending genetic counseling when ordering genetic testing in this and other cardiomyopathies.

The Johns Hopkins arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) program was established in 1999 with 3 goals: 1) to educate patients and physicians about ARVD/C; 2) to evaluate and manage patients with known or suspected ARVD/C; and 3) to contribute to the body of literature regarding this condition. The program has facilitated the clinical evaluation of over 1,140 patients and follows over 250 families with confirmed disease enrolled in the registry. In-house clinical protocols have been established for managing these families.

The management of ARVD/C patients during pregnancy was 1 of the important clinical issues raised by the authors. Pregnancy among ARVD/C patients in the literature is scarce except for scattered case reports and the important series published by Bauce et al. (3) in 2006. With the proliferation of genetic testing and increased recognition of ARVD/C, earlier diagnoses have become possible. During the 14 years our program has been in existence, we have cared for a considerable number of arrhythmogenic right ventricular dysplasia (ARVD) patients who became pregnant. Each of these patients did well during and following pregnancy. In our center, we advise Holter monitoring at 7 months gestation, integration of the cardiac and obstetrical team in planning for delivery, and echocardiogram and Holter monitoring 3 months postpartum. We agree that for the ARVD/C patient considering pregnancy, it is important to discuss the psychosocial issues surrounding passing on a genetic disease. Fortunately, the penetrance of ARVD is low, the expressivity of disease is variable, and, most importantly, ARVD is associated in most patients with a high quality of life and a near-normal life expectancy.

We would caution the reader regarding the authors' suggestion of in vitro fertilization to conceive embryos without a mutation, if known in the family. This is an expensive and invasive option that is, in our experience, unnecessary. As the authors themselves note, digenic inheritance is not uncommon in ARVD/C (4); therefore, pre-implantation genetic diagnosis may not guarantee that the child will not be at risk of developing disease, limiting possible effectiveness. We advise considerable counseling and caution in utilizing this procedure in the setting of solely hoping to avoid ARVD/C in the offspring. Also, regarding amniocentesis to evaluate for ARVD/C-associated mutations, the risk and benefits of this invasive procedure, including a well-appreciated risk of miscarriage, should be thoroughly discussed.

Marcus et al. (1) provide a tool to update physicians regarding genetic testing options to be utilized in the setting of genetic counseling. We hope, however, that an accurate message is portrayed regarding pregnancy in ARVD/C patients and the use of genetic testing technology in such a setting.

Brittney Murray, MS
Crystal Tichnell, MGC
Cindy James, ScM, PhD
Harikrishna Tandri, MD
***Hugh Calkins, MD**

*Division of Cardiology
The Johns Hopkins Hospital
1800 Orleans Street
Sheikh Zayed Tower 7125R
Baltimore, Maryland 21287-0409
E-mail: hcalkins@jhmi.edu

http://dx.doi.org/10.1016/j.jacc.2013.06.057

REFERENCES

1. Marcus FI, Edson S, Towbin J. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol 2013;61:1945–8.
2. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies. Heart Rhythm 2011;8:1308–39.
3. Bauce B, Daliento L, Frigo G, Russo G, Nava A. Pregnancy in women with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Eur J Obstet Gynecol Reprod Biol 2006;127:186–9.
4. den Haan AD, Tan BY, Zikusoka MN, et al. Comprehensive desmosome mutation analysis in North Americans with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Cardiovasc Genet 2009;2:428–35.

Reply

Pregnancy in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

We thank the members of the Johns Hopkins arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) program for their comments regarding our paper (1). The objective of our paper was to provide complete information to physicians and their patients about the genetics of ARVD/C, including all aspects of the inheritance of ARVD/C. In vitro fertilization was included because this is an option for parents to have a child without the possibility of the child developing this condition if 1 of the parents has a pathological gene for arrhythmogenic right ventricular cardiomyopathy. We are not advocating this; we are simply indicating that this option exists. As noted in our report (1), this disease is autosomal dominant, and the offspring has a 50% chance of inheriting the disease if 1 of the parents has an abnormal gene. Although the penetrance is variable, the possibility of the disease expression in the offspring of the parent with a known gene defect is definitely present and parents need to be aware of this. If the offspring develops arrhythmogenic right ventricular cardiomyopathy, the parents may feel guilty about having knowingly taken the risk of transmitting the disease.

***Frank I. Marcus, MD**
Sue Edson, BS
Jeffrey A. Towbin, MD

*Department of Cardiology
University of Arizona Heart Center
Sarver Heart Center
1501 North Campbell Avenue
Room 5153
P.O. Box 245037
Tucson, Arizona 85724-5037
E-mail: fmarcus@u.arizona.edu

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REFERENCE

1. Marcus FI, Edson S, Towbin J. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol 2013;61:1945–8.