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MINI-FOCUS ISSUE: PHARMACOGENETICS AND PERSONALIZED MEDICINE

CLINICAL RESEARCH

G-Protein Beta-3 Subunit Genotype Predicts Enhanced Benefit of Fixed-Dose Isosorbide Dinitrate and Hydralazine: Results of A-HeFT

Dennis M. McNamara, Anne L. Taylor, S. William Tam, Manuel Worcel,
Clyde W. Yancy, Karen Hanley-Yanez, Jay N. Cohn, Arthur M. Feldman

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The G-protein beta-3 subunit (GNB3) plays a role in alpha-adrenergic signaling. The 825T allele of GNB3 is far more prevalent in African Americans and is associated with low renin hypertension. We investigated the influence of GNB3 genotype on the therapeutic efficacy of a fixed-dose combination of isosorbide dinitrate and hydralazine (FDC I/H) in A-HeFT (African-American Heart Failure Trial). FDC I/H improved composite score, quality of life, and event-free survival for subjects with the GNB3 TT genotype, but it had minimal impact in subjects with the GNB3 C allele. GNB3 genotype may allow targeting of I/H therapy to subjects most likely to benefit.

■ EDITORIAL COMMENT

Polymorphic Variation in the G-Protein Beta-3 Subunit Gene and Response to BiDil in A-HeFT: Basis for an African-American Pharmacogenetic Advantage to Nitric Oxide Donor Therapy?

Michael R. Bristow

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STATE-OF-THE-ART PAPER

Race, Common Genetic Variation, and Therapeutic Response Disparities in Heart Failure

Mathew R. Taylor, Albert Y. Sun, Gordon Davis, Mona Fiuzat, Stephen B. Liggett,
Michael R. Bristow

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Primarily because of the East African origin of modern humans, individuals of African ancestry (AA) exhibit greater degrees of genetic diversity than more recently established populations, such as those of European ancestry (EA) or Asian ancestry. Those population effects extend to differences in frequency of common gene variants that may be important in heart failure natural history or therapy. For cell-signaling mechanisms important in heart failure, we review and present new data for genetic variation between AA and EA populations. Data indicate that: 1) neurohormonal signaling mechanisms frequently (16 of the 19 investigated polymorphisms) exhibit racial differences in the allele frequencies of variants comprising key constituents; 2) some of these differences in allele frequency may differentially affect the natural history of heart failure in AA compared to EA individuals; and 3) in many cases, these differences likely play a role in observed racial differences in drug or device response.

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CME

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available online. Go to
<http://heartfailure.onlinejacc.org>
to participate.

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**CLINICAL RESEARCH****Sitagliptin Use in Patients With Diabetes and Heart Failure:
A Population-Based Retrospective Cohort Study**

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Daniala L. Weir, Finlay A. McAlister, Ambikaipakan Senthilselvan, Jasjeet K. Minhas-Sandhu,
Dean T. Eurich

There is uncertainty around the safety of sitagliptin in patients with type 2 diabetes and heart failure (HF); thus, the authors analyzed data from a national commercially insured U.S. claims database to evaluate the safety of sitagliptin in these patients. After adjustment for administrative and clinical data, the authors found sitagliptin users were not at an increased risk of all-cause death or hospital admission (7.1% vs. 9.2%, adjusted odds ratio: 0.84, 95% confidence interval: 0.69 to 1.03) after incident HF. However, sitagliptin use was associated with an increased risk of hospitalizations for HF (12.5% vs. 9.0%, adjusted odds ratio: 1.84, 95% confidence interval: 1.16 to 2.92).

■ **EDITORIAL COMMENT****Do Dipeptidyl Peptidase-4 Inhibitors Increase the Risk of Heart Failure?**

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Deepak L. Bhatt, Matthew A. Cavender

**Albuminuria Is Independently Associated With Cardiac Remodeling,
Abnormal Right and Left Ventricular Function, and Worse Outcomes in
Heart Failure With Preserved Ejection Fraction**

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Daniel H. Katz, Jacob A. Burns, Frank G. Aguilar, Lauren Beussink, Sanjiv J. Shah

Although albuminuria is associated with a worse prognosis in heart failure and preserved ejection fraction (HFpEF), the relationship between albuminuria and cardiac structure/function in HFpEF has not been well studied. This study measured urinary albumin-to-creatinine ratio (UACR) and performed a comprehensive echocardiography in a prospective study of 144 patients with HFpEF. We found that a higher UACR is associated with greater left ventricular (LV) mass, lower pre-load recruitable stroke work, worse LV global longitudinal strain, greater right ventricular (RV) hypertrophy, and lower RV fractional area change. Albuminuria, possibly through its association with generalized endothelial dysfunction, is associated with increased RV and LV remodeling and dysfunction in HFpEF.

 [SEE ADDITIONAL CONTENT ONLINE](#)■ **EDITORIAL COMMENT****A New Direction for Albuminuria: An Enigmatic Multibiomarker**

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Jalal K. Ghali

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