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Impact of Ethnicity and Race on ACE-I Response in Heart Failure

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Racial and ethnic differences in therapeutic response to pharmacotherapy were raised in the field of heart failure (HF) just over 2 decades ago by the results of the Vasodilator-Heart Failure Trials (V-HeFT) trials. V-HeFT I demonstrated that Hydralazine-Isosorbide (H-I) therapy resulted in significant reductions in mortality in African Americans compared to placebo, but not in Caucasians (1). The follow-up study V-HeFT II confirmed these results and further demonstrated that ACEI were of greater benefit in Caucasians (2). Based on these results, African-American Heart Failure Trial (A-HeFT) trial was designed to study the effects on clinical outcomes of the fixed combination of isosorbide dinitrate plus hydralazine to standard therapy in African American patients with heart failure. It demonstrated that isosorbide dinitrate plus hydralazine increased survival and improved symptoms. These results lead to the FDA approval of a HF therapy in a specific racial group (3). H-I is currently recommended for all black patients with NYHA Class III-IV Heart failure in addition to optimal medical therapy and for all patients with heart failure who are intolerant of ACEI/ARB (4).

In this issue of the Journal, Eshtehardi P et al. (5) attempts to further delineate our understanding of the racial/ethnic difference in the treatment of heart failure. In this retrospective, multi-center propensity score matched study of 618 patients with heart failure with reduced ejection fraction (HFrEF) the authors evaluated the effect of ACEI therapy on all cause-mortality and heart failure hospitalizations between 3 racial/ethnic groups, Hispanics, Caucasians and African Americans. The study included patients who self identified racial/ethnic group,

were of similar socioeconomic background, had EF < 35% and were all on beta blocker therapy therapy.

After the authors performed propensity score matching and stratified by racial/ethnic group they observed a distinct benefit from ACEI use in Hispanics. In Caucasian and African American patients ACEI use was associated with a non-significant reduction in all cause mortality, 9.2% vs 10.3% and 12.4% vs 17.8% for ACEI vs No-ACEI respectively. However in Hispanics the use of ACEI therapy resulted in a surprising 67% reduction in all cause-mortality (9.8% vs. 28.4%; HR: 0.033, p = 0.018).

Before discussing the impact of the manuscript by Eshtehardi P et al on the understanding and management of heart failure in Hispanic patients, it will be important to summarize the existent data of heart failure in Hispanics.

Hispanics represent the fastest growing racial/ethnic group in the US, yet are largely underrepresented in clinical trials. The Hispanic population is a heterogeneous group that is identified by a common language, yet from widely different geographical regions. In the US the Hispanic population includes people of European (Spain), Caribbean, Central and South American ancestry. Although it is unclear if there are significant differences between Hispanics of different geographic ancestry, unobserved or unknown differences in this heterogeneous population may affect the response to HF therapies. Hispanics carry a high burden of CV risk factors, often higher than other racial/ethnic groups. Diabetes mellitus, obesity, tobacco use, uncontrolled BP (6), dyslipidemia and metabolic syndrome are more prevalent in the Hispanic population (7). The Hispanic population also suffers unique barriers to

health care including language, lack of health insurance, acculturation and cultural beliefs.

Data from Get With the Guidelines – Heart Failure registry (GWTG-HF) (8) and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) (9) demonstrated racial/ethnic disparities with regard to heart failure performance measures. Hispanics are less likely to have assessment of left ventricular function (10), less likely to be prescribed ACEI/ARB at discharge and are less likely to receive complete discharge instructions. These discrepancies highlight the significant need for strategies to improve the care provided to Hispanics with HF. In addition, a study of 561 patients with heart failure from a Heart Failure Disease Management Program (Jackson Medical Hospital in Miami, Florida) demonstrated that Hispanics patients with heart failure and systolic dysfunction had an 82% use of ACE inhibitors (21 % on target doses) and an 89% use of beta-blockers (21 % on target doses) (11). The percentage of Hispanics adhering to the medication increased by the second appointment, but decreased discretely at the next follow up visits. While ACEI use was relatively high in Hispanics they were less likely to achieve target doses for the ACEI/ARB when compared to African Americans (12).

Despite the limitations, the paper by Eshtehardi P et al in the Journal is of interest as it provides data on clinical outcomes utilizing life saving heart failure therapies in an Hispanic population

However, these results must be tempered because of several limitations of the data and the design of the study.

First, the reduction in mortality was significantly greater than the one observed in the landmark Studies of Left Ventricular Dysfunction (SOLVD) (13) and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (14) trials, which were done prior to the era of Guideline Directed Medical Therapy (GDMT), 16% and 27% reduction respectively.

In both landmark trials the reduction in mortality was driven by reductions in mortality due to progression of heart failure, whereas these data showed a decrease in all cause mortality. The limitations of the study design did not allow for adjudication of CV or HF deaths, which must be taken into consideration. The lack of difference in hospitalizations for heart failure may be a clue to the fact that these patients did not die from heart failure. Furthermore the cohort of patients prescribed ACEI may represent a population of patients that were more compliant, routinely followed with health care professionals and ultimately received better management of other contributing comorbid conditions. Of note, the mortality rate in the untreated Hispanic cohort was significantly higher compared with the untreated white and African American patients, 28.4% vs. 10.3% and 17%, respectively, suggesting the Hispanic population in this study were at significantly higher risk, possibly due to differences in background guideline therapies.

Second, in the era of modern medicine, a placebo controlled randomized trial of ACEI therapy would be unethical. As such the use of propensity score matching is a reasonable alternative, however limitations remain. Propensity score matching can reduce the number of confounders and control for some baseline differences, unfortunately initial selection bias cannot be eliminated. Furthermore variables not

included in the propensity score may still affect the outcome and other unseen variables may bias the results. As a result of the retrospective analysis the authors were unable to assess outcomes based on ACEI dose or compliance. The use of other HF therapies such as mineralocorticoid receptor antagonists (MRA), which have been shown to be prescribed more commonly in Hispanics (8), cardiac resynchronization therapy (CRT) or digoxin were also not studied. While the authors included diabetes, one of the strongest predictors for outcome in HF, body-mass-index (BMI) was not included. In the Candesartan in Heart Failure – Assessment of Mortality and Morbidity (CHARM) trial (15), BMI was a strong predictor of outcome in HF patients and obesity is a prevalent CV risk factor in the Hispanic population.

Interestingly upon performing multivariate analysis in the matched population ACEI use was found to be an independent predictor of lower all-cause mortality in only Hispanics (HR: 0.33, p = 0.018), conversely a physician documented NYHA Functional class III / IV was an independent predictor of higher mortality in Hispanics (HR: 2.99, p = 0.04). It is unclear why NYHA Class was not a predictor of mortality in Caucasians and African Americans. In an analysis of the CHARM trial NYHA Class was a strong predictor of CV death and hospitalization, which included almost exclusively Caucasian and African American patients (15). This lack of effect in Caucasians and African Americans may be a result of difference in background therapy, in the CHARM trial slightly more than 50% of patients were on a beta-blocker, where as in this study all patients were required to be on BB. The propensity score matched data did not demonstrate an improvement in hospital

admissions in this trial even in the Hispanic cohort. Interestingly recent data from the GWTG-HF program seems to contradicts these findings, in the GWTG-HF population Hispanics had higher readmission rates and lower mortality compared with Caucasians with heart failure, and similar to African American patients (16). The in GTWG-HF population the higher readmission rates could be attributed to fewer Hispanic patients receiving complete discharge instructions, resulting in lower compliance with dietary restrictions and adherence to medical therapy. However the lower mortality in Hispanics in the GTWG-HF population was present even in the setting of lower ACEI use.

Upon reading this paper the question one asks is simple; does this change our management? Fundamentally the answer must be no. The authors have shown once again that ACEI therapy improves outcome in patients with heart failure, whether ACEIs preferentially benefit Hispanics with heart failure remains to be determined. The data presented here should remind us that all patients benefit from GDMT, while some may benefit more than others from certain therapies, our responsibility is to ensure that all patients receive optimal medical therapy and seek to eliminate disparities in our practice and in the use of evidence based therapies.

References:

1. Cohn JG, Archibald DG, Ziesches S, Franciosa JA et al. Effect of Vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. NEJM 1986; 314: 1547-1552.
2. Cohn JN, Johnson G, Ziesches S, Cobb F, Francis G, Tristani F et al. A Comparison of enalapril with hydralazine-isosorbide in treatment of chronic congestive heart failure. NEJM 1991; 325:303-310.
3. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks Heart Failure. N Engl J Med. 2004;351:2049-2057.
4. Yancy CW, Jessup M, Bozkurt B, Butler J et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:3240-e327.
5. Eshtardi P, Pamerla M, Mojadidi K, Goodman-Meza D, Hovnanian N, Gupta A, Lupercio F, Mazurek JA, Zolty R. Addition of Angiotensin-Converting Enzyme Inhibitors to Beta-Blockers Has a Distinct Effect on Hispanics Compared to African-Americans and Whites with Heart Failure and Reduced Ejection Fraction: A Propensity Score Matching Study. J Card Fail 2015: XXX-XXX.
6. Campbell PT, Krim SR, Lavie CJ and Ventura HO. Clinical characteristics, treatment patterns and outcomes of Hispanic hypertensive patients. Prog Cardiovasc Dis 2014;57(3):244-52

7. Vivo RP, Krim SR, Cevik C, Witteles RM. Heart Failure in Hispanics. J Am Coll Cardiol 2009;53:1167-175.
8. Yancy CW, Fonarow GC, LaBresh KA et al. Disparate quality of care for black and Hispanic heart failure patients: a report from Get with the Guidelines – Heart Failure (GWTG-HF) (abstr). J Card Fail. 2007;13(suppl 2):S157
9. Albert NM, Fonarow GC, Abraham WT et al. Predictors of delivery of hospital-based heart failure patient education: a report from OPTIMIZE-HF. J Card Fail 2007; 13:189-198.
10. Correra-de-Araujo, Stevens B, May E et al. Gender differences across racial and ethnic groups in the quality of care for acute myocardial infarction and heart failure associated with comorbidities. Womens Health Issues. 2006;16:44-55.
11. Hebert K, Beltran J, Tamariz L et al. Evidence-based medication adherence in Hispanic patients with systolic heart failure in a disease management program. Conges Heart Fail 2010;16(4): 175-80.
12. Ventura HO, Pina I. Heart failure in Hispanic patients: coming together? Congest Heart Fail. 2010; 16(4): 187-8.
13. The SOLVD Investigators. Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions. N Engl J Med 1992;327:685-91
14. The CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. N Engl J Med 1987;316:1429-1435.

15. Pocock TJ, Wang D, Pfeffer MA, Yusuf S, McMurray JSU, Swedberg KB et al. Predictors of Mortality and Morbidity in patients with chronic heart failure. Eur Heart J. 2006;27:65-75.

16. Vivo RP, Krim SR, Lian L, Hernandez AF, Eapa ZJ et al. Short and long term rehospitalization and mortality for heart failure in 4 racial/ethnic populations. J Am Heart Assoc. 2014; 16:3(5): e001134