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Differences in Incidence, Pharmacogenetics, Treatment and Socioeconomic factors in Heart Failure Outcomes between Sub-Saharan Blacks and White Patients

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ABSTRACT

This review addresses the disparity in the phenotype of heart failure with respect to incidence, genetics, response to therapy as well as the socio-economic factors affecting heart failure indices between sub-Saharan blacks and white patients and attempts to propose solutions.

Keywords: Heart failure, outcomes, racial differences, therapy

Introduction

Heart failure is an important cause of morbidity and mortality. The prevalence of congestive heart failure in the United States in 2012 was estimated at over 5.8 million and is expected to hit close to 8.5 million persons by 2030 with the greatest increases occurring in its aging population[1]. As a direct result of this, total medical costs are expected to exceed $53 billion by 2030. In the United States, a country with considerable ethnic diversity, the prevalence of heart failure is projected to be highest among blacks in 2030, than among white Hispanic and other non-Hispanic nonblack patients, (3.6% vs 2.3% and 2.4% respectively) suggesting intrinsic ethnic differences in the genotype, phenotype and/or socioeconomics of heart failure in this country. Comparable heart failure data in developing countries, specifically sub-Saharan Africa are sparse. but the INTER-CHF study, designed to compare mortality variation amongst different world regions found that heart failure mortality was highest in Africa (34%), almost 4 times that in South America (9%) and the middle East (9%).[2] These heart failure participants from Africa were more likely to be younger, sicker (be in NYHA IV), less likely to be due ischemic heart disease,[3,4] have lower literacy levels, less likely to have health insurance and less likely to be on beta blockers, a key component of guideline directed medical care, than participants from other regions[5] once again suggesting key intrinsic and extrinsic factors affecting heart failure all the way from its etiology to treatment. We take two populations that are markedly different: sub-Saharan Africa and the White world and compare and contrast them both.

Incidence and Etiology.

In the United States, heart disease has been the commonest cause of death since 1921[6] [7]and it is estimated that roughly 127.8 million people in the USA above the age of 20 years have some form of cardiovascular disease. Specifically for heart failure, it was estimated that over 56 million people were living with heart failure across 204 countries. In America, coronary heart disease, hypertension, diabetes mellitus, obesity and smoking accounted for 52 % of incident heart failure with population attributable risks highest for coronary artery disease and hypertension[6]. Similar numbers are not available for sub-Saharan as a bloc but individual results from certain registry studies suggest different etiologies. The THESUS-HF study suggested that the cause of heart failure was mostly due to hypertension (45.4%) and rheumatic heart disease (14.3%). Importantly, ischemic heart disease (7.7%) was not a common cause of heart failure [3]although this may be changing. In the most recent study for which we have data, acute coronary syndrome constituted 1.2% of medical admissions in public multispecialty hospitals[8]. These findings were similar across the region as the South of Soweto cohort study also suggested that dilated cardiomyopathy and hypertensive heart disease were responsible for up to 68% of cases of heart failure[9]. In an East African demographic study, the top 3 causes of heart failure were rheumatic heart disease (32%), cardiomyopathy (25.2%) and hypertensive heart disease (17.6%). In that study, only 2.2% of heart failure was attributable to ischemic heart disease.

It is projected that >7 million persons will have heart failure by the year 2025 and over 8 million by the year 2030 with the prevalence of heart failure rising with age[1]. In the United States, the prevalence of heart failure will also likely increase across different ethnicities with the highest projected prevalence remaining among blacks (3.6% by 2030) while it is expected that the lowest prevalence will be among white Hispanic and non-Hispanic and non-black patients (2.3% and 2.4% by 2030 respectively). In the INTER-CHF study, a prospective study that enrolled HF patients from 108 centers in 16 countries, participants from Africa tended to be younger but more likely to be in NYHA class IV[5].

Pharmacogenetics:

Several genetic factors are present which may influence the development of heart failure in blacks and/or their response to standard guideline directed medical therapy. Genetic polymorphisms which impact the natural history of heart failure or drug responses to treatment exist and for a genetic polymorphism to contribute to a racial difference in response to drug therapy, depends on the magnitude of the effect of that gene polymorphism, its frequency within the racial population and the difference between the frequency of the particular gene polymorphism and a non-racially selected population[10].

Multiple, functionally significant, polymorphisms of genes affecting adrenergic signaling system have been found in the β-1 adrenoceptor gene (Arg389Arg) mutation, the G-protein receptor kinase type 5 gene (GRK5) Gln41Leu mutation, the G-protein β-3 subunit (GNB3) 825 C/T and the α2c deletion have been identified and may affect response to known therapies. Individuals homozygous for the Arg389Arg β -1 adrenoceptor (BAR-1) mutation have greater blood pressures responses to atenolol than individuals homozygous for the Gly389Gly mutation[11] and show a greater reduction in exercise heart rate in whites than blacks and that the BAR-1 receptor Arg389Arg was independently associated with a greater reduction in exercise heart rate area under the curve[12].. Also, in heart failure patients, Arg389 homozygotes treated with bucindolol had a 34% reduction in mortality or hospitalization while Gly389 carriers had no clinical response to bucindolol compared with placebo[13]. The fact that, of all ethnic groups studied, blacks may have the lowest incidence of the Arg389Arg mutation may be at least partly responsible for the reduced sensitivity to beta blockers in this population[14]. Similarly, allele frequencies of the other genes involving the adrenergic system differ between blacks and whites. The α2c deletion is more common in blacks but rare in whites, and in one functional study blacks had a greater heart rate response to the cold pressor test than whites. This ethnic difference was removed after adjusting for the α2c deletion polymorphism and the GNB3 polymorphism suggesting that these genetic variants contributed significantly to the ethnic differences in sympathetic mediated heart rate responses[15]. The same holds true for the GRK5 Leu41 variant and the GNB3 825T allele which are more common in blacks than in whites. The GNB3 T allele is associated with increased adrenergic tone and may be one of the mechanisms by which blacks have a

higher prevalence of hypertension than whites[16] and have a higher heart rate response to stress[15]. In one heart failure cohort, the A-HEFT trial, significant gene-gene interactions were noted with reduced event free survival in patients who had both GRK5Leu41 allele and GNB3 825 C allele (Hazard ratio = 6.38) and the Arg389Arg genotype also had a markedly adverse impact on event free survival of heart failure patients for subjects co-inheriting the GNB3 TT genotype (% event free survival at one year for Arg389Arg vs Gly389 = 66% vs 86%, p = 0.002)[17].

Table 1: Selected genetic polymorphisms and their effects on heart failure and responses to drug therapy.

Genetic Polymorphism		Effects
B-1 Adrenoceptor gene	Arg389Gly Commoner in whites	Arg389 shows ↑BP response to atenolol and ↑ reduction in HR AUC, Arg389 homozygotes had ↓hospitalization and mortality when on bucindolol
Adrenergic receptor 2C Insertion322-325Deletion	A2C deletion more common in Blacks	↑HR rate response to cold pressor test than whites, ↑norepinephrine lowering by bucindolol in heart failure
Guanine nucleotide β3 subunit	GNβ3 C825T GNβ3 825T allele more common in blacks than whites	Associated with ↑ adrenergic tone and ↑HR response to stress,
Endothelial nitic oxide synthase gene (Glu298Asp)	Glu298 polymorphism is more frequent in Blacks	May be partly responsible for improved response to the hydralazine/isosorbide fixed dose combination.

Genetic heterogeneity also exists for the endothelial nitric oxide synthase gene (eNOS). The prevalence of eNOS variants differs between Black and white cohorts with the Asp298 variant being more common in Caucasians (34.5%) than in African-Americans(15.5%)[18]. The Asp298 variant of the eNOS gene has a shorter half-life in endothelial cells and has been associated with poorer event free survival in heart failure [19]. This does not suggest that this single nucleotide polymorphism of the eNOS gene contributes to the worsened heart failure outcomes in Blacks. Of interest, however, was that the positive effect of a fixed dose combination of hydralazine/isosorbide dinitrate was primarily in subjects with the eNOS Glu298Glu genotype which predominates in Black subjects. This suggests that genetic heterogeneity may preferentially affect response to heart failure medication[20] and may explain why blacks respond so well to the hydralazine/isosorbide dinitrate fixed dose combination.

While the renin angiotensin system is extremely important in heart failure and drugs that act on it: namely the angiotensin converting enzyme inhibitors, angiotensin receptor blockers , angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists all have favorable effects in heart failure therapy, there are no data to support a racial-genetic interaction for drug response may be blunted in African-American heart failure populations[10].

Treatment Response:

The use of guideline directed medical therapy (GDMT) in the treatment of heart failure is one of the fundamental parts of our armamentarium in the battle against heart failure. This involves use of four classes of drugs: the beta blockers, the angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers(ARB)/angiotensin receptor-neprilysin inhibitors (ARNI), the mineralocorticoid receptor antagonists (MRA) and the sodium glucose cotransporter-2 inhibitors (SGLT-2 inhibitors).[21,22].

ACEI were found to reduce mortality in severe congestive heart failure decades ago[23] when the CONSENSUS trial showed an up to 50% reduction in mortality in patients with heart failure by enalapril compared with placebo. This was also associated with a significant improvement in NYHA class, a reduction in heart size and reduced requirement for other medications.[23]. There were also reductions in hospitalization rates as well in patients with asymptomatic reductions in ejection fraction.[24] . Similar beneficial effects were noted by the ARB's [25]. These drugs work by inhibiting the renin angiotensin aldosterone system and induce vasodilation.[26] They also reduce cardiac remodeling and reduce sodium and water retention as well. In sub-Saharan Africa similar beneficial effects were of the ACE inhibitors were found on mortality and hospitalization days[27,28].

Beta blockers, on the other hand, primarily antagonize the effects of catecholamines, leading to a reduction in heart rates and blood pressures and therefore reduce myocardial oxygen demand. They reduce mortality by up to 35% and hospitalization rates by 31%.[29,30]. Not many studies studying the effect of beta blockers on heart failure have been done in sub-Saharan Africa. Recognizing the possible importance of the sympathetic nervous system inhibition, Ajayi et al tested the hypothesis that concurrent inhibition renin-angiotensin system with enalapril and alpha1 adrenergic blockade may be superior to enalapril alone. They showed an improvement in exercise time in both groups but the group with the combination had a better improvement in exercise time[31,32]. This was a small study and the follow up was over 4 weeks. Larger randomized trials will be required to further evaluate this.

The mineralocorticoid receptor antagonists(MRA) block mineralocorticoid receptors and concurrent aldosterone activity leading to less sodium retention and fibrosis and they effect an improvement in mortality and hospitalizations[33,34]. To my knowledge no trials of the

effect of these MRA's have been done in sub-Saharan Africa. However, Vardeny and colleagues, using data from the RALES study noted that African-Americans with heart failure exhibited more hypokalemia with spironolactone compared with non-African-American patients (potassium <3.5 mmol/l; 17.9% vs 5.6%; P<0.001) and spironolactone reduced the composite end point of death + hospitalization in non-African American patients but not in African-Americans.[35].

SGLT-2 is expressed in segment 1 of the proximal convoluted tubule of the kidney where it is responsible for 90% of glucose reabsorption in the kidney. The SGLT-2 inhibitors were mainly used to treat diabetes mellitus but were found to have excellent cardiovascular benefits in the diabetics treated. They increase natriuresis, improve energy metabolism probably by facilitating the use of ketone bodies, improve cardiac remodeling and inhibit the sympathetic nervous system[36]. Like the other members of the big four in GDMT, they led to a 13% reduction in all cause death and a 14% reduction in cardiovascular death, a 26% relative reduction in the combined risk of cardiovascular death or first hospitalization for heart failure, in patients with reduced ejection fraction, as well as a 25% decrease in the combined end point of hospitalizations and cardiovascular mortality[37]. SGLT2 inhibitors also reduced the risk of composite cardiovascular death or hospitalization and all-cause mortality in patients with minimally reduced or preserved ejection fraction[38]. In a pooled analysis of the DAPA-HF and DELIVER trials, dapagliflozin decreased the risk of the primary endpoint to the same extent in Black (HR:0.69; 95% CI: 0.47 -1.02) and white patients (HR: 0.73; 95% CI: 0.61 – 0.88). The beneficial effects and favorable safety profile of dapagliflozin were consistent across the range of left ventricular ejection fractions in both black and white patients[39].

No mention of racial differences in the response to heart failure drugs would be complete without mentioning the hydralazine/isosorbide combination. The hydralazine isosorbide dinitrate combination exerts its effects by reducing afterload and enhancing cardiac output. Its mortality reducing effects first came to light in the VHEFT study. In this study, the use of hydralazine/isosorbide dinitrate led to a mortality risk reduction of 36% by 3 years. Also left ventricular ejection fraction also rose significantly in the hydralazine/isosorbide dinitrate treated group but not in the placebo or prazosin groups[40]. In a subsequent study investigating the use of a fixed dose of isosorbide dinitrate with hydralazine compared to placebo in Blacks with heart failure, the study was terminated early due to the significantly higher mortality rate in the placebo group that the fixed dose combination group (10.2% vs 6.2%, P = 0.02). There was a 43% reduction in all-cause mortality (HR; 0.57; p+ 0.01), 33% relative reduction in the rate of first hospitalization for heart failure (16.4% vs 22.4%, P = 0.001) and an improvement in quality of life[41]. To date, this remains the only drug approved for treatment of congestive heart failure on the basis of race.

MORTALITY AND RISK FACTORS.

According to the 2024 AHA report on Heart Disease and Stroke Statistics, heart disease has been the leading cause of death in the United States since 1921 and on the basis of data from 2017-2020, 6.7 million Americans ≥ 20 years of age had heart failure[6]. This has increased from approximately 6 million. The prevalence of heart failure is expected to increase by 46% from 2012 to 2030, affecting > 8 million people ≥ 18 years of age. The total percentage of the population with heart failure is expected to rise from 2.4% to 3.0% in 2030. The main risk factors were coronary heart disease (20%), cigarette smoking (14%), hypertension (20%) diabetes mellitus (12%) and obesity (12%). The annual attributable mortality rate per 100,000 declined from 141.0 in 1999 to 108.3 in 2012, after which it increased to 121.3 in 2019. Mortality rate declines have been attributed to the use of evidence-based approaches to treat heart failure with reduced ejection fraction. And it is estimated that initiation of quadruple therapy reduces the hazard of cardiovascular death or heart failure hospitalization by up to 62% resulting in up to 1.4-6.3 additional years of life[6,42]. Until recently no data was available from sub-Saharan Africa and the authors of the INTER-CHF[43] and THESUS-HF are to be commended for giving us data to not only understand the scope of heart failure in sub-Saharan Africa but also lays a foundation on which to gauge progress and the effects of intervention.

The THESUS-HF was a prospective, multicenter, international observational survey conducted in 12 hospitals in 9 countries in eastern, western, central and southern regions of sub-Saharan Africa, while the INTER-CHF study was also a multicenter cohort study comprising of patients recruited from 16 countries in Africa, the Middle East and South America. Participants from Africa (Nigeria, Uganda, Sudan, South Africa and Mozambique) were more likely to be younger and were less likely to have health or medication insurance or be on beta blockers than participants from other regions.[5]. The most common risk factor for heart failure in the African cohort was hypertensive heart disease (35%). This was followed by ischemic heart disease (20%) which was common in South Africa and Sudan, then followed by idiopathic dilated cardiomyopathy (14.1%) and rheumatic heart disease (7.2%)[43]. The one-year all-cause mortality rate in the African countries combined was 26.4% and was highest in Sudan (42%) but lowest in South Africa (11.7%) while heart failure hospitalization was highest in Sudan (37.3%) and lowest in Uganda (6.0%). [43]

SOCIOECONOMIC AND GEOGRAPHIC FACTORS

Low socioeconomic status is a known risk factor for mortality worldwide [44]and Inverse correlations have been noted between national gross domestic product-purchasing power parity (a determinant of health expenditure and affordability and availability of medications) and the intra-hospital mortality rate for different countries[45]. Not a lot of data is available in sub-Saharan Africa, but a representative sample in a hospital in southwestern Nigeria found that the cost of heart failure was approximately ₦319,200 ($2128.00) per patient per year in 2014 which would roughly translate to ₦2,941,960 in today's money[46]. Inpatient costs, comprising hospitalization, tests, medications, and procedures accounted for roughly 46% of these total costs. In general, this is out of the reach of the average

Nigerian citizen. In the United states, cost per heart failure hospitalization ranged from mean charges of $7094 to $9769[47]. While larger than in Africa, payment in Nigeria is largely made through out-of-pocket payments as only a small proportion of patients have access to health insurance. This disparity in ability to pay significantly impacts access to, and quality of care obtained. Other regional factors affecting disparity of health care in congestive heart failure include increased difficulty with transport in the rainy season further reducing health care access and contributing to late disease presentation. an association with endomyocardial fibrosis.

Conclusions And Future Directions

Significant differences exist in the syndrome of heart failure between the United States and sub-Saharan Africa from the standpoint of etiology, incidence and prevalence, access to therapy, response to therapy, and the presence of differing heart failure phenotypes and social and geographic factors. While sub-Saharan Africa is heterogenous in terms of all these factors, by far the greatest impact for improvement will have to come from social interventions which impact people on individual, interpersonal, community and societal levels. This will require co-operation between health care providers and government policy makers at all levels including, in the sub-Saharan setting, traditional rulers, as well as stakeholders in the academic, finance and business sectors. Evidence based structural interventions would have to be developed as well as means for measuring their impact on predefined indices of heart failure incidence.[48]. These interventions, once developed and found to work, may be deployed in different areas after modification to suit the geographical area. While dealing with social issues is vital to the success of reducing the impact of heart failure in Africa, other areas need to be explored. Enough data exists to suggest that the heart failure phenotype may be different in the sub-Saharan population not just from an access and utilization of drug therapy standpoint, but also in the response to standard heart failure therapy. We highlighted differences in drug response to standard quadruple goal directed medical therapy in this article and it may be necessary to perform multicenter, randomized, placebo-controlled trials in this region as well as improved participation in these trials. This will require extensive education of the population to remove ingrained suspicion. Finaly, another factor that will be of significant impact is the development of a nationwide health insurance scheme which has been started in a minority of countries but with differing degrees of uptake.

Conflict of Interest:

None

References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. May 2013;6(3):606-19. Doi:10.1161/HHF.0b013e318291329a
2. Dokainish H, Teo K, Zhu J, et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health*. Jul 2017;5(7):e665-e672. Doi:10.1016/S2214-109X(17)30196-1
3. Damasceno A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med*. Oct 8 2012;172(18):1386-94. Doi:10.1001/archinternmed.2012.3310
4. Dzudie A, Barche B, Nkoke C, et al. Survival rate and predictors of 36-month mortality in patients with heart failure in Sub Saharan Africa: insights from the Douala Heart Failure Registry (Do-HF). *Cardiovasc Diagn Ther*. Oct 2022;12(5):577-588. Doi:10.21037/cdt-22-166
5. Dokainish H, Teo K, Zhu J, et al. Heart Failure in Africa, Asia, the Middle East and South America: The INTER-CHF study. *Int J Cardiol*. Feb 1 2016;204:133-41. Doi:10.1016/j.ijcard.2015.11.183
6. Martin SS, Aday AW, Almarzooq ZI, et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. Feb 20 2024;149(8):e347-e913. Doi:10.1161/CIR.0000000000001209
7. Shay CM, Gooding HS, Murillo R, Foraker R. Understanding and Improving Cardiovascular Health: An Update on the American Heart Association's Concept of Cardiovascular Health. *Prog Cardiovasc Dis*. Jul-Aug 2015;58(1):41-9. Doi:10.1016/j.pcad.2015.05.003
8. Isezuo S, Sani MU, Talle A, et al. Registry for Acute Coronary Events in Nigeria (RACE-Nigeria): Clinical Characterization, Management, and Outcome. *J Am Heart Assoc*. Jan 4 2022;11(1):e020244. Doi:10.1161/JAHA.120.020244
9. Sliwa K, Wilkinson D, Hansen C, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet*. Mar 15 2008;371(9616):915-22. Doi:10.1016/S0140-6736(08)60417-1
10. Taylor MR, Sun AY, Davis G, Fiuzat M, Liggett SB, Bristow MR. Race, common genetic variation, and therapeutic response disparities in heart failure. *JACC Heart Fail*. Dec 2014;2(6):561-72. Doi:10.1016/j.jchf.2014.06.010
11. Sofowora GG, Dishy V, Muszkat M, et al. A common beta1-adrenergic receptor polymorphism (Arg389Gly) affects blood pressure response to beta-blockade. *Clin Pharmacol Ther*. Apr 2003;73(4):366-71. Doi:10.1016/s0009-9236(02)17734-4
12. Kurnik D, Li C, Sofowora GG, et al. Beta-1-adrenoceptor genetic variants and ethnicity independently affect response to beta-blockade. *Pharmacogenet Genomics*. Oct 2008;18(10):895-902. Doi:10.1097/FPC.0b013e328309733f
13. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc Natl Acad Sci U S A*. Jul 25 2006;103(30):11288-93. Doi:10.1073/pnas.0509937103
14. Xie HG, Dishy V, Sofowora G, et al. Arg389Gly beta 1-adrenoceptor polymorphism varies in frequency among different ethnic groups but does not alter response in vivo. *Pharmacogenetics*. Apr 2001;11(3):191-7. Doi:10.1097/00008571-200104000-00002
15. Kurnik D, Friedman EA, Muszkat M, et al. Genetic variants in the alpha2C-adrenoceptor and G-protein contribute to ethnic differences in cardiovascular stress responses. *Pharmacogenet Genomics*. Sep 2008;18(9):743-50. Doi:10.1097/FPC.0b013e3282fee5a1
16. Dorr M, Schmidt CO, Spielhagen T, et al. beta-blocker therapy and heart rate control during exercise testing in the general population: role of a common G-protein beta-3 subunit variant. *Pharmacogenomics*. Sep 2010;11(9):1209-21. Doi:10.2217/pgs.10.88
17. Johnson AE, Hanley-Yanez K, Yancy CW, Taylor AL, Feldman AM, McNamara DM. Adrenergic Polymorphisms and Survival in African Americans With Heart Failure: Results From A-HeFT. *J Card Fail*. Jul 2019;25(7):553-560. Doi:10.1016/j.cardfail.2019.04.007
18. Tanus-Santos JE, Desai M, Flockhart DA. Effects of ethnicity on the distribution of clinically relevant endothelial nitric oxide variants. *Pharmacogenetics*. Nov 2001;11(8):719-25. Doi:10.1097/00008571-200111000-00011
19. McNamara DM, Holubkov R, Postava L, et al. Effect of the Asp298 variant of endothelial nitric oxide synthase on survival for patients with congestive heart failure. *Circulation*. Apr 1 2003;107(12):1598-602. Doi:10.1161/01.CIR.0000060540.93836.AA
20. McNamara DM, Tam SW, Sabolinski ML, et al. Endothelial nitric oxide synthase (NOS3) polymorphisms in African Americans with heart failure: results from the A-HeFT trial. *J Card Fail*. Apr 2009;15(3):191-8. Doi:10.1016/j.cardfail.2008.10.028
21. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. May 3 2022;79(17):1757-1780. Doi:10.1016/j.jacc.2021.12.011
22. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll*

Cardiol. May 3 2022;79(17):e263-e421. Doi:10.1016/j.jacc.2021.12.012

23. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. Jun 4 1987;316(23):1429-35. Doi:10.1056/NEJM198706043162301
24. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. Sep 3 1992;327(10):685-91. Doi:10.1056/NEJM199209033271003
25. Ostergren JB. Angiotensin receptor blockade with candesartan in heart failure: findings from the Candesartan in Heart failure--assessment of reduction in mortality and morbidity (CHARM) programme. *J Hypertens Suppl*. Mar 2006;24(1):S3-7. Doi:10.1097/01.hjh.0000220400.08128.fa
26. Kourek C, Briasoulis A, Papamichail A, et al. Beyond Quadruple Therapy and Current Therapeutic Strategies in Heart Failure with Reduced Ejection Fraction: Medical Therapies with Potential to Become Part of the Therapeutic Armamentarium. *Int J Mol Sci*. Mar 7 2024;25(6)Doi:10.3390/ijms25063113
27. Ajayi AA, Balogun MO. Sustained beneficial effects of enalapril in Africans with congestive heart failure. *Int J Cardiol*. Oct 1990;29(1):55-61. Doi:10.1016/0167-5273(90)90273-8
28. Ajayi AA, Osodi OO, Akintomide AO. The influence of captopril on intrahospital mortality and duration of hospitalization in Nigerians with congestive heart failure. *Int J Cardiol*. Sep 1992;36(3):341-3. Doi:10.1016/0167-5273(92)90304-I
29. Eichhorn EJ, Bristow MR. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. *Curr Control Trials Cardiovasc Med*. 2001;2(1):20-23. Doi:10.1186/cvm-2-1-020
30. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA*. Mar 8 2000;283(10):1295-302. Doi:10.1001/jama.283.10.1295
31. Ajayi AA, Sofowora GG, Balogun MO. Concurrent alpha 1 adrenergic blockade and angiotensin converting enzyme inhibition in the treatment of congestive heart failure. *Int J Cardiol*. Dec 6 1996;57(2):173-6. Doi:10.1016/s0167-5273(96)02799-4
32. Ajayi AA, Sofowora GG, Adigun AQ, Asiyanbola B. Adjunctive sympathoplegic therapy to ACE inhibition in Blacks with congestive heart failure: a comparison of alpha-1 with beta-1 blockade on exercise tolerance and cardiac sympathovagal reflex activity. *Ethn Dis*. Winter 2003;13(1):71-9.
33. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. Sep 2 1999;341(10):709-17. Doi:10.1056/NEJM199909023411001
34. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. Jan 6 2011;364(1):11-21. Doi:10.1056/NEJMoa1009492
35. Vardeny O, Cavallari LH, Claggett B, et al. Race influences the safety and efficacy of spironolactone in severe heart failure. *Circ Heart Fail*. Sep 1 2013;6(5):970-6. Doi:10.1161/CIRCHEARTFAILURE.113.000530
36. Xie Y, Wei Y, Li D, Pu J, Ding H, Zhang X. Mechanisms of SGLT2 Inhibitors in Heart Failure and Their Clinical Value. *J Cardiovasc Pharmacol*. Jan 1 2023;81(1):4-14. Doi:10.1097/FJC.0000000000001380
37. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet*. Sep 19 2020;396(10254):819-829. Doi:10.1016/S0140-6736(20)31824-9
38. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. Sep 3 2022;400(10354):757-767. Doi:10.1016/S0140-6736(22)01429-5
39. Butt JH, Docherty KF, Claggett BL, et al. Dapagliflozin in Black and White Patients With Heart Failure Across the Ejection Fraction Spectrum. *JACC Heart Fail*. Apr 2023;11(4):375-388. Doi:10.1016/j.jchf.2022.11.014
40. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. Jun 12 1986;314(24):1547-52. Doi:10.1056/NEJM198606123142404
41. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. Nov 11 2004;351(20):2049-57. Doi:10.1056/NEJMoa042934
42. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. Jul 11 2020;396(10244):121-128. Doi:10.1016/S0140-6736(20)30748-0
43. Karaye KM, Dokainish H, ElSayed A, et al. Clinical Profiles and Outcomes of Heart Failure in Five African Countries: Results from INTER-CHF Study. *Glob Heart*. 2021;16(1):50. Doi:10.5334/gh.940
44. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *Lancet Glob Health*. Jun 2019;7(6):e748-e760. Doi:10.1016/S2214-109X(19)30045-2
45. Ajayi A, Sofowora GG, Ladipo G. Explaining Heart Failure Hyper-mortality in Sub Saharan Africa: Global Genomic and Environmental Contribution Review. *Journal of The Nationa;l Medical Association*. 2020;112(2):141-157.

46. Ogah OS, Stewart S, Onwujekwe OE, et al. Economic burden of heart failure: investigating outpatient and inpatient costs in Abeokuta, Southwest Nigeria. *PLoS One*. 2014;9(11):e113032. Doi:10.1371/journal.pone.0113032
47. Osenenko KM, Kuti E, Deighton AM, Pimple P, Szabo SM. Burden of hospitalization for heart failure in the United States: a systematic literature review. *J Manag Care Spec Pharm*. Feb 2022;28(2):157-167. Doi:10.18553/jmcp.2022.28.2.157
48. Brown AF, Ma GX, Miranda J, et al. Structural Interventions to Reduce and Eliminate Health Disparities. *Am J Public Health*. Jan 2019;109(S1):S72-S78. Doi:10.2105/AJPH.2018.304844

