EDITORIAL

JAMES B. YOUNG, MD
Chair, Endocrinology and Metabolism Institute,
and Staff, Department of Cardiovascular Medicine,
Critical Care Center, and Transplantation Center,
Cleveland Clinic; Professor of Medicine and
Executive Dean, Cleveland Clinic Lerner College
of Medicine of Case Western Reserve University,
Cleveland, OH

Evolution of heart failure management: Miles to go

The woods are lovely, dark and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep.

—Robert Frost, "Stopping by Woods on a Snowy Evening"[1]

F ROST'S WORDS ARE SIMPLE yet elegant. They can be interpreted many ways. I see the allegory of life as a journey in this poem. The passage, like the woods, is beautiful, but there is a long, long way to go.

And so it is with the treatment of heart failure. There is beauty in our understanding of the syndrome's physiologic complexities and natural history, and of effective treatments uncovered. Still, we've a monstrous climb ahead to get to the summit of this clinical challenge in order to start a real descent.

■ THE PAST, PRESENT, AND FUTURE OF HEART FAILURE THERAPY

Okwuosa et al,[2] in this issue of the *Journal*, have capably summarized the ABCs of treating heart failure with reduced ejection fraction (also called systolic heart failure), approaching the subject from a perspective on past, present, and future therapies. They summarize heart failure interventions with a guideline-based philosophy, pointing out that these care paths are supposed to be evidence-based. They observe that in the 1960s the standard of care was digitalis, diuretics (furosemide first became available in 1967), and rest. That was

about all we had for this problem.

There are now many drugs, devices, and operations that help patients with heart failure. But they never really cure the disease or, more aptly, the syndrome—and therapies are supposed to cure. This limitation of present therapies is important, given the disturbing epidemiology of heart failure, its economic cost, and the suffering of patients. That burden is well detailed.

In addition to curing, the overarching goals of treatment generally are to ameliorate distressing symptoms and to prevent comorbidities. In heart failure with reduced ejection fraction, we want to prevent premature death, stroke, myocardial infarction, congestive states, hospitalization, renal insufficiency, renal failure, cachexia, inanition, feebleness, and respiratory distress, among others.

The ABC mnemonic of Okwuosa et al will help caregivers remember the basics. It is important, however, to put algorithms into proper perspective and to look toward the future.

■ PROBLEMS WITH EVIDENCE-BASED MEDICINE

Several problems with our current heart failure treatments are rooted in how we perform clinical trials, arguably the premier method of determining truth in clinical practice and the foundation of evidence-based medicine.[3,4]

Do the trials represent real-world practice?

Were the clinical trials that led to regulatory approval and professional society endorsement of the therapies that we prescribe in our offices done in the same sorts of patients as those in our waiting rooms asking for help? Perhaps, for the most part, they have been. And thus, Ok-

Several problems with current heart failure treatments are rooted in how we perform clinical trials

wuosa et al have crafted a work relevant to all of us and every patient.

But I believe there are major gaps in the types of participants enrolled in trials, eg, underrepresentation of certain racial and ethnic groups, not to mention the relative paucity of women. The very elderly (a rapidly growing population) have largely been ignored as well, and participants with significant renal insufficiency, anemia, and diabetes mellitus seem far fewer than what we deal with in a busy clinic.

In addition, Okwuosa et al focus only on patients with reduced left ventricular ejection fraction, a group that makes up only about half of the heart failure crowd.

What about quality of life and other important outcomes?

Clinical trials in heart failure with reduced ejection fraction have generally focused on major clinical end points (primarily, but not exclusively, mortality), to the exclusion of quality of life. Though sometimes included in trials, quality-of-life metrics generally get relegated to second-class seats or 'tween-deck steerage. Perhaps that is because measuring quality of life can be time-consuming and difficult.

Yet, in the words of sociologist William Bruce Cameron, not everything that counts can be counted, and not everything that can be counted counts. That goes for quality of life.

Lies, damned lies, and *P* values

Quandaries in data management and analysis include what to do about trial dropouts, study power, precision of statistical analysis, intention-to-treat principles, and choice of the *P* value that defines significance (or not) for any end point observation. Of course, there are myriad sophisticated mathematical and statistical reasons to justify why we don't simply count on-treatment participants or allow imputation of results when patients or results drop out, forcing us to worship at the altar of $P < .05$.

A review of the *P* value concept[5] recently appeared with an accompanying editorial by Kyriacou[6] that concluded that "the automatic application of dichotomized hypothesis testing based on prearranged levels of statistical significance should be substituted with a more complex process using effect estimates, confidence intervals, and even *P* values, thereby permitting scientists, statisticians, and clinicians to use their own inferential capabilities to assign scientific significance."[6]

How many great treatments have we tossed out because of rigid reliance on old-fashioned approaches to determining therapeutic evidence? Many treatments studied have had great results in a minority of patients in clinical trials but did not have a major positive (or negative) impact on the overall cohort (with lack of primary end point statistical significance). And what to do when the primary end point is a neutral or negative one but secondary end points are positive? Why not focus more attention on those patients benefiting from an intervention despite the overall results of any trial?

Dilemmas of trials

Other issues are that clinical trials cost too much, and that recruitment and follow-up take too long. Intercurrent therapies (and guidelines) can emerge that jeopardize the trial itself or make observations untimely. The dilemma of stacking therapies one on top of another, often making patient compliance impossible, is another problem with clinical trials. Yet this is how we get to the ABCs.

■ A NEW WAY TO DO TRIALS

The information provided by Okwuosa et al is useful and encouraging, but too many gaps exist in our heart failure therapies to permit us to celebrate with exuberance. Too many patients still suffer, too many die too young, and the costs are still too great.

Perhaps the future of therapeutic development should embrace different and better ways to demonstrate real value (relying on the equation of value equals outcomes meaningful to patients, divided by cost) of therapies, including the old, the new, the trashed and the underdeveloped. More creative data analysis to reexamine the current tools on the shelf and the ones tried but discarded is essential.

A position paper from the Cardiovascular Round Table of the European Society of Cardiology concluded that "a coordinated effort involving academia, regulators, industry

Too many patients still suffer, too many die too young, and the costs are still too great

and payors will help to foster better and more effective conduct of clinical cardiovascular trials, supporting earlier availability of innovative therapies and better management of cardiovascular diseases."[7]

Lauer and D'Agostino,[8] also in an editorial, argued for innovative methods of doing clinical trials and discovering truth about therapies that are applicable to the future of developing treatments for heart failure with reduced ejection fraction. They noted that "the randomized registry trial represents a disruptive technology" and wondered if it will be "given serious consideration as a way to resolve the recognized limitations of current clinical-trial design."[8]

Indeed, conducting megatrials with existing megadatabases using a registry format could help. Registries emerging from early adaptive trial design efforts, particularly when Bayesian analysis theory is applied, might help inform clinical experience faster and more efficiently. Bayesian analysis is a statistical approach that attempts to estimate parameters of an underlying distribution of events in an ongoing fashion based on the observed distribution. A clinical trial of stem cell therapies could, at the end of the trial, be turned into a multicenter registry that would continue to inform us about the more real-world application of newer treatment approaches.

Though the therapeutic cupboard for heart failure is certainly not bare, as Okwuosa et al point out, it is wanting. Let's look for new therapeutic ABCs differently. We should be attacking the real challenge—curing the disease processes that cause the syndrome. Yes, there are miles to go before we sleep. ■

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ADDRESS: James B. Young, MD, Cleveland Clinic, Education Institute, NA21, 9500 Euclid Avenue, Cleveland, OH 44195; youngj@ccf.org

IKE S. OKWUOSA, MD
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

OLUSEYI PRINCEWILL, MD, MPH
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

CHIEMEKE NWABUEZE, MD
Georgetown University School of Medicine, Washington, DC

LENA MATHEWS, MD
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

STEVEN HSU MD
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

NISHA A. GILOTRA, MD
Director, Heart Failure Bridge Clinic, Advanced Heart Failure/Transplant Cardiology, Division of Cardiology; Assistant Professor of Medicine, The Johns Hopkins Hospital, Baltimore, MD

SABRA LEWSEY, MD, MPH
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

ROGER S. BLUMENTHAL, MD
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

STUART D. RUSSELL, MD
Division of Cardiology, The Johns Hopkins Hospital, Baltimore, MD

The ABCs of managing systolic heart failure:
Past, present, and future

ABSTRACT

Heart failure management is complex and constantly evolving. The American College of Cardiology and the American Heart Association (ACC/AHA) last issued evidence-based guidelines in 2013, and since then, new drugs and devices have been developed. This review presents an evidence-based approach to current heart failure management.

KEY POINTS

Most patients with systolic heart failure (also called heart failure with reduced ejection fraction) should receive either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. Most should also receive a beta-blocker (carvedilol, metoprolol succinate, or bisoprolol).

If symptoms persist or progress despite these treatments, an aldosterone receptor antagonist (spironolactone or eplerenone) is recommended.

Since the publication of the ACC/AHA guidelines in 2013, the combination of sacubitril and valsartan has been approved, as has ivabradine.

Patients with advanced heart failure should be identified early for consideration of resynchronization therapy, an implantable cardiac defibrillator, digoxin, a left ventricular assist device, or heart transplant.

B-type natriuretic peptide levels can be used to guide therapy.

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MANAGING HEART FAILURE is a challenge. To aid clinicians in this task, the American College of Cardiology Foundation (ACC) and the American Heart Association (AHA) publish evidence-based guidelines, most recently in 2013.[1] Since then, new drugs and devices have been shown to improve survival and reduce hospitalizations.

This paper reviews the ABCs of outpatient management of systolic heart failure (or heart failure with reduced ejection fraction), including the results of major trials and recommendations.

A | **A common and serious condition**
Angiotensin
Aldosterone

A common and serious condition

Heart failure is a debilitating syndrome that takes a significant physical and mental toll on those affected.

And it is common. An American age 40 or older faces a 20% lifetime risk of heart failure.[1] An estimated 5.1 million Americans have clinical signs and symptoms of heart failure, and 900,000 new cases are diagnosed each year.[2] By 2030 the prevalence of heart failure is projected to increase by 46%, and 9 million Americans will have been diagnosed with it.[2]

The severity of heart failure can be described using either the functional classification devised by the New York Heart Association (NYHA; **Table 1**) or the stages defined by

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TABLE 1

Heart failure stages and functional classes

NYHA class I	NYHA class II	NYHA class III	NYHA class IV
No physical limitations	Slight limitation of physical activity	Marked limitation of physical activity	Symptoms at rest

Stage A	Stage B	Stage C	Stage D
Patients at risk for heart failure No structural disease	Structural disease No heart failure symptoms	Structural disease Heart failure symptoms	End-stage disease

NYHA = New York Heart Association

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the ACC and AHA.[1,3] Though survival rates have improved, there is a direct correlation between worsening symptoms and death.[4]

Heart failure is the leading cause of hospitalizations annually. It accounts for $30 billion in healthcare costs, with direct medical costs accounting for 68% and another $1.8 billion associated with clinic visits, most often with primary care providers. By 2030, the cost is projected to increase by 127% to $69.7 billion—$244 per person in the United States.[2]

ACE inhibitors

The renin-angiotensin-aldosterone system has been studied for over 100 years.[5]

In heart failure with reduced ejection fraction, this system is upregulated as an adaptive mechanism to maintain hemodynamic homeostasis.[6–8] However, prolonged activation of the renin-angiotensin-aldosterone system can lead to deleterious cardiovascular effects such as myocyte hypertrophy, myocardial fibrosis, sodium conservation, and fluid overload.[8,9] Angiotensin II is a potent vasoconstrictor and plays a role in cardiovascular remodeling, leading to worsening progression of heart failure.[6]

CONSENSUS (the Cooperative North Scandinavian Enalapril Survival Study) examined the effect of the angiotensin-converting enzyme (ACE) inhibitor enalapril on survival in 253 patients with NYHA class IV heart failure. Participants were randomized to receive either enalapril or placebo. At 6 months, the mortality rate was 26% in the enalapril group vs 44% in the placebo group, an 18% absolute risk reduction and a 41% relative risk reduction (P = .002). At 12 months, the relative risk reduction in mortality was 30% (P = .001).[10]

SOLVD (the Study of Left Ventricular Dysfunction) extended the use of ACE inhibitors to all patients with heart failure, not just those in NYHA class IV. It randomized 1,284 patients with heart failure of any NYHA class and an ejection fraction less than 35% to receive either enalapril or placebo, and demonstrated a 16% relative risk reduction in mortality in the enalapril group, with mortality rates of 36% vs 39.7% (P = .0036).[11]

Recommendations. The benefits of ACE inhibition have been demonstrated in patients with mild, moderate, and severe heart failure. Thus, the guidelines recommend ACE inhibitors (**Table 2**) for all patients with heart failure with reduced ejection fraction.[1]

Angiotensin II receptor blockers

Angiotensin II receptor blockers (ARBs) (**Table 3**) have been proven to be suitable alternatives for patients with heart failure with reduced ejection fraction who cannot tolerate ACE inhibitors.

Val-HefT (the Valsartan HF Trial)[12] randomized 5,010 patients in a double-blind fashion to receive either valsartan or placebo, with background therapy that included beta-blockers, digoxin, diuretics, and ACE inhibitors. There was a 13% reduction of the combined primary end point of mortality and morbidity and a 24% reduction in heart failure hospitalizations in the valsartan group.[12]

Subgroup analysis compared patients on the basis of use of ACE inhibitors and beta-blockers at study entry. Valsartan had a favorable effect in the subgroups using beta-blockers alone, ACE inhibitors alone, and neither drug. However, when patients received all

An American age 40 or older faces a 20% lifetime risk of heart failure

three (a beta-blocker, an ACE inhibitor, and valsartan), the mortality rate was significantly increased (*P* = .009).[12] This finding conflicted with those of other studies, which found a small benefit of combining an ACE inhibitor and an ARB.

CHARM-Added (the Candesartan in HF Assessment of Reduction in Mortality and Morbidity trial)[13] investigated whether adding the ARB candesartan to an ACE inhibitor would improve clinical outcomes. In the study, 2,548 patients in NYHA class II, III, or IV with a left ventricular ejection fraction of less than 40% who were receiving ACE inhibitors were randomized to either candesartan or placebo. The addition of candesartan resulted in a significant reduction in cardiovascular mortality and heart failure hospitalizations, but with the downside of higher rates of hyperkalemia and serum creatinine elevation.[13]

Recommendations. The 2013 guidelines recommend that ARBs be used in patients who cannot tolerate an ACE inhibitor due to cough. However, routine combined use of ARBs, ACE inhibitors, and aldosterone antagonists is not recommended and may cause harm.[1]

Aldosterone receptor antagonists

Elevated levels of aldosterone lead to fluid retention, loss of magnesium and potassium, and myocardial fibrosis.

RALES (the Randomized Aldactone Evaluation Study)[14] tested the hypothesis that the aldosterone receptor antagonist spironolactone (25 mg daily) would reduce deaths from all causes in patients with severe heart failure receiving standard medications including an ACE inhibitor. RALES included 1,663 patients in NYHA class III or IV with a left ventricular ejection fraction of 35% or less, randomized to receive 25 mg of spironolactone or matching placebo. This study found a 30% relative risk reduction and an 11% absolute risk reduction in all-cause mortality, a 31% relative risk reduction and a 10% absolute risk reduction in cardiac mortality, and 30% fewer cardiac-related hospitalizations in the spironolactone group.[14]

Eplerenone, an aldosterone receptor antagonist that lacks the antiandrogenic side effects of spironolactone, has also been shown to be beneficial. Its efficacy in patients with

TABLE 2

Angiotensin-converting enzyme inhibitors for managing heart failure

Generic name	Dosing range
Benazepril	5–40 mg once a day
Captopril	6.5–50 mg three times a day
Enalapril	2.5–20 mg twice a day
Fosinopril	5–40 mg once a day
Lisinopril	2.5–40 mg once a day
Quinapril	5–20 mg once a day
Ramipril	1.25–10 mg once a day
Trandolapril	1–4 mg once a day

TABLE 3

Angiotensin II receptor blockers for managing heart failure

Generic name	Dosing range
Candesartan	4–32 mg once a day
Losartan	25–150 mg once a day
Valsartan	20–160 mg twice a day

left ventricular systolic dysfunction was first established in postmyocardial infarction patients.[15]

EMPHASIS-HF (the Eplerenone in Mild Patients Hospitalized and Survival Study in Heart Failure)[16] broadened the application of eplerenone (and aldosterone antagonists in general), investigating the effects of eplerenone in 2,737 NYHA class II patients, regardless of ischemic etiology. The composite end point of cardiovascular death or heart failure hospitalization occurred in 18.3% of the eplerenone group vs 25.9% of the placebo group (*P* < .001). A total of 12.5% of patients in the eplerenone group died, compared with 15.5% in the placebo group (*P* = .008). Hospitalizations were also fewer in the eplerenone group.

Recommendations. The 2013 guidelines recommend aldosterone receptor antagonists

TABLE 4

Aldosterone receptor antagonists for managing heart failure

Generic name	Dosing range
Eplerenone	25–50 mg once a day
Spironolactone	12.5–25 mg once or twice a day

TABLE 5

Angiotensin-neprilysin inhibition for managing heart failure

Generic name	Dosing range
Sacubitril-valsartan	24–26 mg, 49–51 mg, or 97–103 mg twice daily If tolerated for 2–4 weeks, double the daily dose until target dose of 97–103 mg twice daily is reached For patients converting from an ACE inhibitor, this medication should be started 36 hours after discontinuation of the ACE inhibitor

Routinely combining ARBs, ACE inhibitors, and aldosterone antagonists is not recommended

(**Table 4**) for patients with NYHA class II, III, or IV heart failure who have an ejection fraction of 35% or less, to reduce morbidity and mortality (class IA recommendation).[1] The guidelines also recommend that these agents not be used in patients with renal insufficiency (serum creatinine > 2.5 mg/dL in men or > 2.0 mg/dL in women; an estimated glomerular filtration rate < 30 mL/min/1.73 m^2); or a serum potassium level above 5 mmol/L.[1]

Angiotensin-neprilysin inhibitor (the future)
Research has identified neprilysin as another potential target in the treatment of heart failure and has sought to combine inhibition of angiotensin and neprilysin.

Neprilysin, a neutral endopeptidase, is associated with degradation of several natural vasoactive peptides such as natriuretic peptide, bradykinin, and adrenomedullin. Neprilysin inhibition increases these substances and counters the neurohormonal overactivation that leads to vasoconstriction, sodium retention, and cardiac remodeling.[17]

The ARB valsartan has been combined with the neprilysin inhibitor sacubitril to create the first angiotensin-neprilysin inhibitor (ARNI) (**Table 5**). The combination was selected to minimize the potential for angioedema.

PARADIGM-HF (the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial)[17] examined whether combined angiotensin-neprilysin inhibition was superior to ACE inhibition alone with enalapril in patients with chronic heart failure.

In PARADIGM-HF, 10,521 patients with NYHA class II, III, or IV heart failure were randomized to receive either sacubitril-valsartan or enalapril. The group receiving sacubitril-valsartan had significantly fewer deaths from cardiovascular causes and heart failure hospitalizations.[17] An improvement in quality of life and NYHA functional class was also observed in the sacubitril-valsartan group.[17]

Sacubitril-valsartan underwent priority review by the US Food and Drug Administration and has been approved. Currently, it is indicated for the treatment of heart failure with reduced ejection fraction and NYHA class II, III, or IV symptoms. It should be avoided in patients who have previously experienced angioedema with an ACE inhibitor or ARB, in patients receiving aliskiren for diabetes, and in patients with hypersensitivity reactions to either of its components. Simultaneous use of sacubitril-valsartan and an ACE inhibitor should be avoided, and a washout period is recommended when transitioning from an ACE inhibitor to this combined agent.

B Beta-blockers BNP

Beta-blockers

In heart failure, there is increased sympathetic activation and associated elevations in norepinephrine levels, which may lead to deleterious long-term effects on cardiac function and structure. Beta-adrenergic receptor blockade is now known to be cardioprotective, but it was not always so; beta-blockers used to be contraindicated in patients with heart failure.

An early experience using beta-blockers in heart failure was described in 1975.[18,19] The first study to report a survival benefit of treating systolic heart failure with a beta-blocker was published in 1979.[20] Later, small controlled tri-

als demonstrated a reduction in heart failure symptoms and improvement in left ventricular function and in NYHA functional class.[21] Larger clinical trials have demonstrated a tremendous survival benefit with beta-blockers in heart failure, specifically carvedilol, extended-release metoprolol, and bisoprolol.

The US Carvedilol Heart Failure Study Group trial[22] evaluated whether beta-blocker use in heart failure patients would reduce the rates of morbidity and mortality.[22] The trial included 1,094 patients with symptomatic heart failure for at least 3 months and a left ventricular ejection fraction of 35% or less on background therapy including vasodilators, ACE inhibitors, and digoxin. Patients were randomized to receive either carvedilol or placebo. Carvedilol use was associated with a dramatic 65% risk reduction in mortality (7.8% with placebo vs 3.2% with carvedilol, *P* < .001) and a 27% risk reduction in hospitalizations (19.6% vs 14.1%, *P* = .036), leading to early trial termination.

CIBIS-II (the Cardiac Insufficiency Bisoprolol Study II)[23] investigated the effects of beta-blockers on survival and morbidity. CIBIS-II included 2,647 NYHA class III or IV patients with a left ventricular ejection fraction less than 35% on background medical therapy that included diuretics and ACE inhibitors. This trial was also terminated early, after demonstrating a significant survival benefit with bisoprolol.

MERIT-HF (the Metoprolol Extended Release Randomized Intervention Trial in Congestive Heart Failure)[24] evaluated if once-daily metoprolol would lower mortality rates in patients with symptomatic heart failure. The study enrolled 3,991 NYHA class II–IV patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Like the previous two beta-blocker trials, MERIT-HF was terminated early, as it demonstrated a 34% reduction in all-cause mortality (7.2% risk of death per patient-year vs 11.0%, *P* = .00009).

The beta-blocker trials have shown that when added to background therapy, beta-blockers improve survival and reduce hospitalizations. However, when prescribing a beta-blocker, it is important to understand that not all beta-blockers are equal in the treatment of heart failure.

TABLE 6

Beta-blockers for managing heart failure

Generic name	Dosing range
Bisoprolol	1.25–10 mg once a day
Carvedilol	3.125–50 mg twice a day
Metoprolol succinate	12.5–200 mg once a day

COMET (the Carvedilol or Metoprolol European Trial)[25] was the only head-to-head randomized control trial evaluating clinical outcomes in patients receiving carvedilol or metoprolol tartrate (not metoprolol succinate). In COMET, 1,511 patients with NYHA class II, III, or IV heart failure with a left ventricular ejection fraction of 35% or less were randomized to carvedilol or metoprolol tartrate. The primary end point of all-cause mortality occurred in 34% of the carvedilol group and 40% of the metoprolol tartrate group (*P* = .0017). There was no significant difference with regard to the composite end point of mortality and all-cause admissions.

Recommendations. The 2013 guidelines give a class IA recommendation for starting a beta-blocker (carvedilol, bisoprolol, or metoprolol succinate, **Table 6**) in patients with current or prior symptoms of heart failure.[1] Beta-blockers should be initiated with caution or avoided in patients with acutely decompensated heart failure with evidence of fluid overload.

Brain-type natriuretic peptide

Brain-type natriuretic peptide (BNP) or its amino-terminal cleavage product (NT-proBNP) originates in cardiomyocytes and is released by several triggers, most commonly cardiomyocyte stretch in the setting of volume or pressure overload.[26] The biologic significance of BNP includes natriuresis and vasodilation, renin-angiotensin system inhibition, and sympathetic nervous system modulation.[26]

TIME-CHF (the Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive HF)[27] investigated whether 18-month outcomes would be better if treatment were guided by N-terminal BNP levels rather than by symptoms. The BNP-guided

A washout period is recommended when transitioning from an ACE inhibitor to valsartan-sacubitril

TABLE 7

I$_f$ inhibition for managing heart failure

Generic name	Dosing range
Ivabradine	5–7.5 mg twice a day Initial dosing is 5 mg by mouth twice daily for 2 weeks Dose may be increased 5 mg to maintain a resting heart rate between 50 and 60 beats per minute Maximum daily dose 15 mg/day

strategy was not associated with a reduction in hospitalization or a survival benefit.

BATTLESCARRED (the NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death trial)[28] in 2009 showed that a BNP-guided management strategy significantly reduced mortality rates in patients under age 75 compared with standard medical therapy.

PROTECT (the Use of NT-proBNP Testing to Guide HF Therapy in the Outpatient Setting study)[29] also showed that a BNP-guided strategy was superior to usual care and was associated with reduced cardiovascular events and improved quality of life.[29]

GUIDE IT-HF (the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure study), currently ongoing, is designed to assess the safety, efficacy and cost-effectiveness of a biomarker-guided strategy in 1,100 high-risk patients with heart failure with reduced ejection fraction.

Recommendations. The 2013 ACC/AHA guidelines give a class IA recommendation for the use of BNP to support clinical decision-making, particularly in cases of clinical uncertainty.[1] BNP can also be used to establish prognosis or disease severity in chronic heart failure and to achieve optimal dosage of goal-directed medical therapy for euvolemic patients followed in a structured heart failure program.[1]

C | **Clinics**
Chronotropy

Heart failure clinics

Continuity of care upon discharge from the hospital is currently in a state of evolution. Those diagnosed with heart failure can now experience more comprehensive posthospital care by virtue of disease management clinics. The name may vary by institution, but whether it is called a "diuresis clinic," "bridge clinic," or "heart failure clinic," the goal is to improve guideline-driven care, educate the patient, and reduce heart failure hospitalizations. Heart failure clinics are designed to provide a smooth transition from inpatient to outpatient care and to encourage patient self-accountability in health maintenance thereafter.

Studies have shown that heart failure clinics are associated with better medication dosing, fewer hospitalizations, and lower healthcare costs.[30–32]

Chronotropy: I$_f$ inhibition

An elevated resting heart rate has been shown to be associated with increased cardiovascular morbidity and mortality.[33] Studies have shown that slowing the heart rate improves myocardial contraction and energy supply and reduces energy expenditure.[34] Ivabradine, a selective I$_f$ (the *f* is for "funny") channel inhibitor, slows the heart rate without other known cardiovascular effects.

SHIFT (the Systolic Heart Failure Treatment With the I$_f$ Inhibitor Ivabradine Trial)[35] investigated whether isolated heart rate reduction with ivabradine would reduce adverse clinical outcomes in patients with symptomatic heart failure. SHIFT randomized 6,505 patients with a left ventricular ejection fraction of 35% or less, in sinus rhythm, with a heart rate of at least 70 beats per minute, on optimal medical therapy, and hospitalized within 12 months of enrollment to receive ivabradine or placebo. The primary end point was a composite of cardiovascular mortality and hospital admission for worsening heart failure. Outcomes varied by heart rates achieved, with the best outcomes in those with the lowest heart rates at trial conclusion.

Ivabradine (**Table 7**) is indicated for patients with symptomatic heart failure with a left ventricular ejection fraction less than 35%, in sinus rhythm, with a resting heart rate of at least 70 beats per minute, and either on a maximally tolerated beta-blocker or with a contraindication to beta-blockers.

Ivabradine should be avoided in patients who are in acute decompensated heart failure

BNP testing is recommended, especially in cases of clinical uncertainty

or are hypotensive (blood pressure < 90/50 mm Hg), as well as in patients with a significant conduction abnormality (sick sinus syndrome, sinoatrial block, third-degree atrioventricular block), hepatic impairment, or bradycardia (resting heart rate < 60 beats per minute).

D Digoxin
Diuretics
Devices

Digoxin

Digoxin has been used in treating systolic heart failure for more than 70 years.[36,37]

DIG (Digoxin Investigative Group trial)[38] evaluated the long-term effect of digoxin on rates of mortality and hospitalization for heart failure over a 3-year period. In patients with a left ventricular ejection fraction less than 45%, digoxin had no effect on overall mortality when combined with diuretics and ACE inhibitors. However, the risk of hospitalization for worsening heart failure was significantly reduced with digoxin treatment.[38]

Recommendations. Digoxin should be considered when patients are on guideline-recommended therapy but heart failure symptoms persist. It is commonly initiated at a dose of 0.125 to 0.25 mg. The target therapeutic range for digoxin is 0.5 to 0.9 ng/mL.[1] Digoxin toxicity can occur in patients with renal impairment, hypokalemia, hypomagnesemia, and hypothyroidism.

The 2013 ACC/AHA guidelines give a class IIA recommendation (treatment is "reasonable") for digoxin in patients with heart failure with reduced ejection fraction unless contraindicated, to decrease hospitalizations for heart failure.[1]

Diuretics

Clinical manifestations of volume overload in patients with heart failure are from excess salt and water retention leading to inappropriate volume expansion in both the vascular and extravascular space. Diuretics (**Table 8**) are the foundation of heart failure treatment. Most patients are first initiated on a combination of a loop diuretic and a low-sodium diet to improve symptoms.

The 2013 ACC/AHA guidelines give a class I recommendation for diuretics in patients

TABLE 8

Diuretic dosing in heart failure

Generic name	Dosing range
Bumetanide	0.5–10 mg daily in one or two doses
Furosemide	20–600 mg daily in one or two doses
Torsemide	10–200 mg once daily

with heart failure with reduced ejection fraction who have evidence of fluid retention, unless contraindicated, to improve symptoms.[1]

Devices: ICDs

Patients with heart failure are at increased risk of sudden death and ventricular arrhythmias.[39] Previously, antiarrhythmic drugs were considered the standard of care for nonsustained ventricular tachycardia after myocardial infarction.

MADIT (the Multicenter Automatic Defibrillator Implantation Trial) investigated whether prophylactic implantation of an internal cardiac defibrillator would improve 5-year survival rates in patients with heart failure. Eligible patients had had a Q-wave or enzyme-positive myocardial infarction within 3 weeks of study entry. They also had had an episode of asymptomatic nonsustained ventricular tachycardia unrelated to an acute myocardial infarction. Additionally, the patients had a left ventricular ejection fraction less than 35%, and inducible, sustained, nonsuppressible ventricular tachyarrhythmia on electrophysiologic testing.[40]

During the study, 15 patients in the defibrillator group died vs 39 in the conventional therapy group ($P = .009$).[40]

MADIT II evaluated the potential survival benefit of a prophylactically implanted defibrillator in the absence of electrophysiologic testing to induce arrhythmias.[41] MADIT II included 1,232 patients with prior myocardial infarctions and a left ventricular ejection fraction of 30% or less. Patients were randomized to receive an implanted cardioverter-defibrillator or conventional medical therapy. The primary end point was death from any cause.[41]

The mortality rate was 19.8% in the conventional therapy group vs 14.2% in the defi-

Heart failure clinics promote better medication dosing, reduce hospitalizations, and lower healthcare costs

brillator group (hazard ratio 0.69, P = .016).[41] Thus, MADIT-II confirmed the benefits of prophylactic implantable cardioverter-defibrillator therapy seen in the original MADIT, and additionally eliminated the need for an electrophysiology test prior to device implantation.

SCD-HeFT (the Sudden Cardiac Death in Heart Failure Trial) evaluated whether amiodarone or a conservatively programmed shock-only, single-lead implanted cardioverter-defibrillator would decrease the risk of death (all-cause) in a population with mild to moderate heart failure with ischemic and nonischemic causes.[42] In this trial, 2,521 patients with an ejection fraction of 35% or less, in NYHA class II or III, and with stable heart failure were randomized to receive a single-chamber implantable cardioverter-defibrillator, amiodarone, or placebo.

There were 244 deaths in the placebo group, 240 deaths in the amiodarone group (P = .53 compared with placebo), and 182 deaths in the defibrillator group (P = .007 compared with placebo).[42]

Recommendations. The 2013 ACC/AHA guideline[1] gives implantable defibrillator therapy a class IA recommendation for the primary prevention of sudden cardiac death in selected patients with nonischemic cardiomyopathy or ischemic cardiomyopathy at least 40 days after a myocardial infarction and 90 days after percutaneous coronary intervention or coronary artery bypass grafting; with a left ventricular ejection fraction of 35% or less; and NYHA class II or III symptoms on chronic goal-directed medical management.

This therapy receives a class IB recommendation for primary prevention of sudden cardiac death to reduce total mortality in selected patients at least 40 days after myocardial infarction with a left ventricular ejection fraction of 30% or less and NYHA class I symptoms while receiving goal-directed medical therapy.

Implantable cardioverter-defibrillators are not recommended in patients who otherwise have a life expectancy of less than 1 year.

Devices:
Cardiac resynchronization therapy

From 25% to 30% of heart failure patients have an intraventricular conduction abnormality,[43,44] which can result in abnormalities of systolic and diastolic function. Biventricular pacing, in which a pacing lead is placed in the coronary sinus in addition to the right atrium and right ventricle, optimizes synchronization of ventricular contraction.[43,44]

MUSTIC (the Multisite Stimulation in Cardiomyopathies study) was a randomized trial designed to assess the efficacy of biventricular pacing (also known as cardiac resynchronization therapy) in heart failure patients.[44] Entry criteria included NYHA class III heart failure for at least 1 month, left ventricular ejection fraction less than 35%, left ventricular end-diastolic diameter greater than 60 mm, and QRS duration longer than 150 ms. Patients were followed up at 9 and 12 months with 6-minute walking distance, peak oxygen consumption, changes in NYHA class, and left ventricular systolic function by echocardiography or radionuclide testing. Quality of life was assessed by the Minnesota Living With Heart Failure Questionnaire.

At 12 months, patients could walk significantly farther in 6 minutes, and their peak oxygen consumption had increased. They also reported significant improvement in quality of life, and NYHA class improved by 25%. MUSTIC was the first study to show a benefit in exercise tolerance, quality of life, improvement in cardiac performance, and reduction in heart failure symptoms with the use of biventricular pacing at 1 year.

MIRACLE (the Multicenter InSync Randomized Clinical Evaluation) validated the findings seen in MUSTIC by using a larger population size and a double-blinded method.[45] Compared with a control group, patients who underwent cardiac resynchronization therapy could walk farther in 6 minutes and scored better in NYHA class, quality of life, and left ventricular ejection fraction.[45]

Recommendations. The 2013 ACC/AHA guidelines[1] give cardiac resynchronization therapy a class IA/B indication for NYHA class II, III, or IV patients on goal-directed medical therapy in sinus rhythm with left ventricular ejection fraction 35% or less, left bundle branch block, and QRS duration of 150 ms or more.[1]

Ivabradine slows the heart rate without other known cardiovascular effects

Devices: Implantable sensors

The future of ambulatory heart failure management may include implantable pulmonary artery pressure sensors.

The CardioMEMS is a permanently implantable pressure measurement system designed to provide daily pulmonary artery pressure measurements in an ambulatory setting with a goal of reducing heart failure-related hospitalizations. Through a transvenous delivery system, an implantable, battery-free sensor is positioned in the distal pulmonary artery.[46,47]

CHAMPION (the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients trial) was one of the first major trials to assess the safety and efficacy of implantable pulmonary artery pressure monitoring systems.[46] The study device was associated with a significant reduction in mean pulmonary artery pressures, fewer heart failure hospitalizations, and better quality of life. The length of stay for heart failure-related hospitalizations was also significantly shorter in the CardioMEMs group.[46]

E | Exercise
End-stage heart failure

Exercise

Patients with heart failure routinely experience a decline in functional capacity. This decline manifests as reduced exercise tolerance and poor quality of life, usually resulting in a physician recommendation to rest and paradoxical deconditioning and possible progression of symptoms.

Several studies have shown that cardiac rehabilitation has improved outcomes in heart failure patients.[48] Cardiac rehabilitation is a supervised program that helps patients with exercise training, healthy living, education, and psychosocial counseling.

HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) is the largest randomized trial performed to determine whether aerobic exercise training reduces all-cause mortality or all-cause hospitalization and improves quality of life in patients with stable heart failure.[49] Although the reduction in end points was initially not statistically significant, after adjusting for highly prognostic predictors of poor

outcomes (cardiopulmonary exercise time, left ventricular ejection fraction, atrial fibrillation, and depression), exercise training was found to reduce the incidence of all-cause mortality or all-cause hospitalization by 11% (P = .03).[49]

Recommendations. Based on the results of HF-ACTION and several smaller studies, the ACC/AHA guidelines give exercise training a class IA recommendation as a safe and effective activity for patients with heart failure who are able to participate, to improve functional status.[1] A class IIA recommendation is given to cardiac rehabilitation for the improvement of functional capacity, exercise duration, quality of life, and mortality rates.[1]

End-stage heart failure: Recognition

Despite adequate titration of goal-directed medical therapy, a portion of patients with heart failure with reduced ejection fraction ultimately progress to stage D, also termed "advanced" heart failure. The 5-year survival rate for patients with heart failure overall is 50%, but the 1-year mortality rate for those with advanced heart failure exceeds 50%.[50]

Because the high rates of morbidity and mortality can potentially be lowered, recognition of heart failure disease progression is imperative so that patients can be promptly referred for therapies such as inotropic infusion, mechanical circulatory support, and cardiac transplant, as well as end-of-life care such as hospice.[1]

The ACC/AHA[1] have published clinical events and findings useful in identifying patients with advanced heart failure:

- Two or more hospitalizations or emergency department visits for heart failure in the past year
- Progressive deterioration in renal function (eg, elevation in creatinine or blood urea nitrogen)
- Weight loss without other cause
- Intolerance to ACE inhibitors due to hypotension or worsening renal function
- Inability to tolerate beta-blockers due to worsening heart failure or hypotension
- Systolic blood pressure often below 90 mm Hg
- Persistent dyspnea with dressing or bathing requiring rest
- Inability to walk one block on level ground due to dyspnea or fatigue

Diuretics are the foundation of heart failure treatment

Diuretics for congestive symptoms
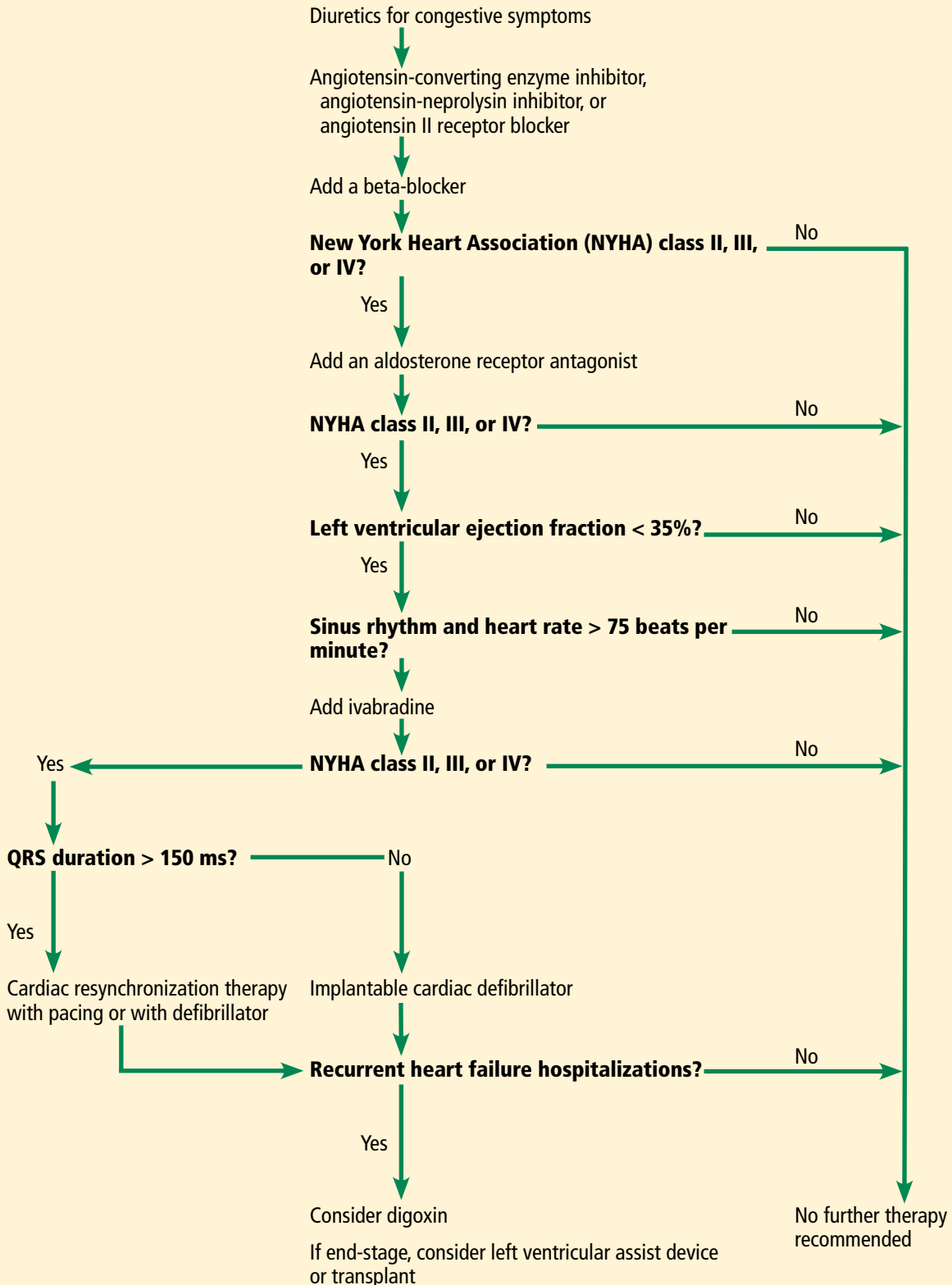
Angiotensin-converting enzyme inhibitor, angiotensin-neprolysin inhibitor, or angiotensin II receptor blocker

Add a beta-blocker

New York Heart Association (NYHA) class II, III, or IV? — No

Yes

Add an aldosterone receptor antagonist

NYHA class II, III, or IV? — No

Yes

Left ventricular ejection fraction < 35%? — No

Yes

Sinus rhythm and heart rate > 75 beats per minute? — No

Add ivabradine

NYHA class II, III, or IV? — No

Yes

QRS duration > 150 ms? — No

Yes

Cardiac resynchronization therapy with pacing or with defibrillator

Implantable cardiac defibrillator

Recurrent heart failure hospitalizations? — No

Yes

Consider digoxin

If end-stage, consider left ventricular assist device or transplant

No further therapy recommended

FIGURE 1. An algorithm for managing heart failure with reduced ejection fraction.

- Recent need to escalate diuretics to maintain volume status, often reaching daily dose equivalent to furosemide more than 160 mg/day or use of supplemental metolazone
- Progressive decline in serum sodium, usually to below 133 mmol/L
- Frequent shocks from implanted cardiac defibrillator.

End-stage heart failure:
Left ventricular assist devices

For patients with refractory heart failure despite optimal medical management, advanced therapies such as heart transplant or ventricular assist devices have been proven to be durable options. These mechanical circulatory support devices "unload" the diseased ventricle and maintain cardiac output to vital organs.[51] They were initially designed as temporary support to allow ventricular recovery or as a bridge to cardiac transplant. However, they have also evolved into permanent ("destination") therapy.[52]

REMATCH (the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive HF trial) was the landmark study that showed that left ventricular assist device implantation resulted in a survival benefit and an improved quality of life in patients with advanced heart failure ineligible for cardiac transplant, compared with medical management.[50] Implantation of a left ventricular assist device was associated with a 27% absolute reduction in the 1-year mortality rate.[50]

Since the National Institutes of Health's artificial heart program was launched in 1964, there has been tremendous progress in the development of mechanical circulatory devices.[50] The results of REMATCH were promising, but the 2-year survival rate was still only 23%, leaving a lot to be desired.

The HeartMate II (Thoratec) trial compared an axial continuous-flow device vs the previously established pulsatile left ventricular assist device, and noted a 2-year survival of 58% with the continuous flow device vs 24% with the pulsatile device (*P* = .008).[53]

ADVANCE (Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure) showed similar efficacy of the HVAD (Heartware), a centrifugal continuous-flow LVAD currently in use.[54]

The next generation of continuous-flow left ventricular assist devices are currently in clinical trials in the United States and include the axial flow MVAD (Heartware) and centrifugal flow Heartmate III (Thoratec).

We emphasize the importance of early identification of patients with advanced disease who may qualify for and benefit from such therapies.

F Failure (less of it)

The management of heart failure is evolving. In the 1960s, the standard heart failure medical regimen included digoxin, diuretics, and the recommendation of rest. This contrasts with the current era, in which medical regimens include neurohormonal blockade, diuretics, and the promotion of physical activity.[55] Since the publication of the 2013 heart failure guidelines, new medical and device options have emerged that have been proven to either improve survival or reduce hospitalizations. The development of clinical guidelines promotes evidence-based practice and overcomes the inertia of practice patterns based on anecdotal evidence.

Several approaches to the management of heart failure have been recommended. A major effort should be made to identify those at risk for heart failure (stage A) and to implement risk factor modification. Treatment of hypertension, diabetes mellitus, and dyslipidemia decreases the risk of heart failure.[1]

For patients with evidence of structural heart disease with and without symptoms, **Figure 1** summarizes a guideline approach to the management of heart failure. It should be stressed that guidelines are meant to guide management, but do not serve as a substitute for sound clinical judgment.

Heart failure is the common final pathway of all cardiac pathology, and understanding the neurohormonal response and maladaptive physiology has led to the development of novel therapeutics and devices. At present, the field of cardiology may not be able to remove the "failure" from heart failure, but we can make every effort to prevent failure of treatment delivery and reduce resource utilization and morbidity associated with this syndrome. ∎

The future of ambulatory heart failure management may include implantable pulmonary artery pressure sensors

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ADDRESS: *Ike Stanley Okwuosa, MD, The Johns Hopkins Hospital, 1800 Orleans Street, Zayed 7125, Baltimore, MD 21287; isokwuosa@gmail.com*