Deep analysis of Heart-Failure treatment, New Drugs but Old Practice (DAO-HFT)

Dr.Taram Asghar[1], Dr.Sana Iqbal[2]

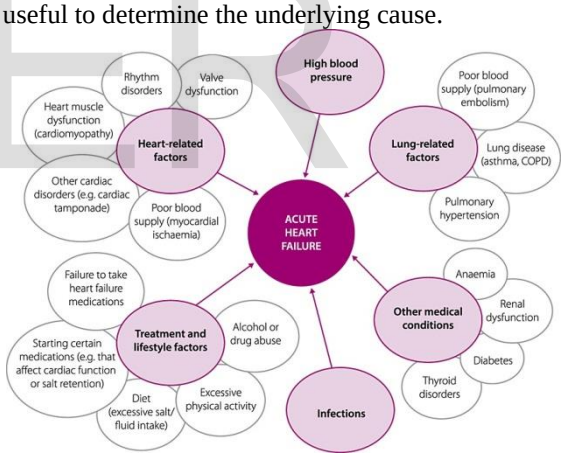
Abstract:
New drugs and devices have emerged for the management of heart failure. Fortunately, there is also clear evidence to guide our decision-making. Heart failure: from research to clinical practice", a collection of selected reviews, which comes out also as a book, covers essentially all important aspects of heart failure, including the pathogenesis, clinical features, biomarkers, imaging techniques, medical treatment and surgical treatments, use of pacemakers and implantable cardioverter defibrillators, and palliative care. The reviews include essential background information, state of the, critical and in-depth analysis, and directions for future researches for elucidation of the unresolved issues. Everyone Interested in heart failure is expected to find this compilation helpful for a deeper understanding of some of the complex issues. This paper will briefly review the diagnosis and initial evaluation of the patient with suspected HF and then describe how newer treatments fit within HF management priorities and strategies. But first, a word about what causes HF.

Keywords
Diagnosis of heart failure • HF • CCF treatment of heart failure • Palliative care of heart failure • Cardiac magnetic resonance imaging in heart failure • Heart failure with reduced ejection fraction, cardiomyopathy.

Introduction:

Heart failure (HF), also known as congestive heart failure (CHF) and congestive cardiac failure (CCF), is when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs. Signs and symptoms of heart failure commonly include shortness of breath, excessive tiredness, and leg swelling.The shortness of breath is usually worse with exercise or while lying down, and may wake the person at night. A limited ability to exercise is also a common feature. Chest pain, including angina, does not typically occur due to heart failure.[1]

Common causes of heart failure include coronary artery disease, including a previous myocardial infarction (heart attack), high blood pressure, atrial fibrillation, valvular heart disease, excess alcohol use, infection, and cardiomyopathy of an unknown cause. These cause heart failure by changing either the structure or the function of the heart. The two types of left ventricular heart failure – heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF) – are based on whether the ability of the left ventricle to contract, or to relax, is affected. The severity of the heart failure is graded by the severity of symptoms with exercise.[2] Heart failure is not the same as heart attack (in which part of the heart muscle dies) or cardiac arrest (in which blood flow stops altogether). Other diseases that may have symptoms similar to heart failure include obesity, kidney failure, liver problems, anemia, and thyroid disease. Diagnosis is based on symptoms, physical findings, and echocardiography. Blood tests, electrocardiography, and chest radiography may be useful to determine the underlying cause.



Improving care for patients with acute heart failure: before ...

Treatment depends on the severity and cause of the disease. In people with chronic stable mild heart failure, treatment commonly consists of lifestyle modifications such as stopping smoking, physical exercise, and dietary changes, as well as medications. In those with heart failure due to left ventricular dysfunction, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or valsartan/sacubitril along with beta blockers is recommended. For those with severe disease, aldosterone antagonists, or hydralazine with a nitrate may be used. Diuretics are useful for preventing fluid retention and the resulting shortness of breath.[8] Sometimes, depending on the cause, an implanted device such as a pacemaker

or an implantable cardiac defibrillator (ICD) may be recommended.[3] In some moderate or severe cases, cardiac resynchronization therapy (CRT) or cardiac contractility modulation may be of benefit. A ventricular assist device (for the left, right, or both ventricles), or occasionally a heart transplant may be recommended in those with severe disease that persists despite all other measures.

Heart failure is a common, costly, and potentially fatal condition. In 2015, it affected about 40 million people globally. Overall around 2% of adults have heart failureand in those over the age of 65, this increases to 6–10%. Rates are predicted to increase. The risk of death is about 35% the first year after diagnosis; while by the second year the risk of death is less than 10% for those who remain alive.This degree of risk of death is similar to some cancers.[4] In the United Kingdom, the disease is the reason for 5% of emergency hospital admissions. Heart failure has been known since ancient times, with the Ebers papyrus commenting on it around 1550 BCE.

Signs and symptoms

A man with congestive heart failure and marked jugular venous distension. External jugular vein marked by an arrow.

Heart failure is a path physiological state in which cardiac output is insufficient to meet the needs of the body and lungs.[4] The term "congestive heart failure" is often used, as one of the common symptoms is congestion, or build-up of fluid in a person's tissues and veins in the lungs or other parts of the body.[4] Specifically, congestion takes the form of water retention and swelling (edema), both as peripheral edema (causing swollen limbs and feet) and as pulmonary edema (causing breathing difficulty), as well as ascites (swollen abdomen).

Heart failure symptoms are traditionally and somewhat arbitrarily divided into "left" and "right" sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation, however people commonly have both sets of signs and symptoms.

Left-sided failure

The left side of the heart receives oxygen-rich blood from the lungs and pumps it forward to the systemic circulation (the rest of the body except for the pulmonary circulation). Failure of the left side of the heart causes blood to back up (be congested) into the lungs, causing respiratory symptoms as well as fatigue due to insufficient supply of oxygenated blood. Common respiratory signs are increased rate of breathing and increased work of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli). [5] Cyanosis which suggests severe low blood oxygen, is a late sign of extremely severe pulmonary edema.

Right-sided failure

Severe peripheral (pitting) edema
Right-sided heart failure is often caused by pulmonary heart disease (cor pulmonale), which is typically caused by difficulties of the pulmonary circulation, such as pulmonary hypertension or pulmonic stenosis.

Physical examination may reveal pitting peripheral edema, ascites, liver enlargement, and spleen enlargement. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by eliciting hepatojugular reflux. If the right ventricular pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength.

Causes

Viral infections of the heart can lead to inflammation of the muscular layer of the heart and subsequently contribute to the development of heart failure. Heart damage can predispose a person to develop heart failure later in life and has many causes including systemic viral infections (e.g., HIV), chemotherapeutic agents such as daunorubicin, cyclophosphamide, and trastuzumab, and abuse of drugs such as alcohol, cocaine, and methamphetamine. An uncommon cause is exposure to certain toxins such as lead and cobalt. [6] Additionally, infiltrative disorders such as amyloidosis and connective tissue diseases such as systemic lupus erythematosus have similar consequences. Obstructive sleep apnea (a condition of sleep wherein disordered breathing overlaps with obesity, hypertension, and/or diabetes) is regarded as an independent cause of heart failure.

Association Between AF and HFrEF
AF and HFrEF, at surface, share many fundamental predisposing risk factors, such as hypertension, diabetes mellitus, ischemic and valvular heart disease, and a predilection for increased incidence in the elderly, as well. Even more interesting is how AF and HFrEF collaborate to promote each other (Figure 1); deeper mechanistic understanding of these underlying pathways may eventually be helpful in disease prevention.

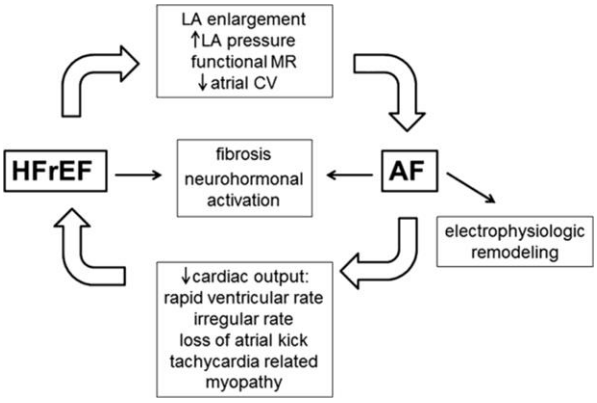


Figure 1. Known relationships between atrial fibrillation and heart failure that contribute to a vicious cycle

Diagnosis

No system of diagnostic criteria has been agreed on as the gold standard for heart failure. The National Institute for Health and Care Excellence recommends measuring brain natriuretic peptide (BNP) followed by an ultrasound of the heart if positive. This is recommended in those with shortness of breath. In those with worsening heart failure, both a BNP and a troponin are recommended to help determine likely outcomes.[7]

In 2015, empagliflozin, an inhibitor of sodium–glucose cotransporter 2 (SGLT2), lowered the com-posite cardiovascular end point in the EMPA-REG trial1 involving patients with type 2 diabetes mellitus who were at increased cardiovascular risk. What was remarkable in that finding was that the benefit was driven by reductions in hos-pitalization for heart failure and cardiovascular mortality but not by a lower frequency of myocar-dial infarction or stroke. Moreover, empagliflozin appeared to slow deterioration in renal function, and the heart-failure benefits persisted in the presence of renal dysfunction. These early obser-vations regarding heart failure were extended and confirmed in two subsequent trials of SGLT2 inhibitors involving patients with type 2 dia- betes: the CANVAS trial of canagliflozin2 and the DECLARE–TIMI 58 trial of dapagliflozin.3 Since these heart-failure benefits were indepen-dent of glucose lowering, it was postulated that SGLT2 inhibitors might be a treatment for heart failure associated with a reduced ejection fraction (i.e., systolic heart failure), regardless of diabetes status.

TABLE 1

Diagnostic testing in the initial evaluation of heart failure[5,7]

Tests	Purpose
CBC, BMP, LFTs, magnesium, calcium	Evaluate the patient's suitability for particular therapies, detect reversible/treatable causes of HF
Lipid profile	Evaluate for comorbidities
TSH	Rule out hypo- and hyperthyroidism
HbA1c	Evaluate for comorbidities
BNP, NT-proBNP	Assist in diagnosis of HF
EKG	Evaluate rate, rhythm, QRS morphology, QRS duration
CXR	Evaluate for comorbidities, evidence of HF
Echocardiogram	Determine EF, evaluate for valvular and other structural heart disease
Noninvasive imaging to detect ischemia (eg, stress testing, etc)	Detect underlying myocardial ischemia
Additional tests for select patient populations	
Ferritin, TIBC, transferrin saturation	Rule out hemochromatosis, anemia
HIV	Evaluate suitability for particular therapies, detect reversible/treatable causes of HF
ANA, Lyme serology	Evaluate for underlying diagnoses
Cardiac MRI	Evaluate for myocardial infiltration (eg, amyloid) or scar tissue from a previous cardiac event

ANA, antinuclear antibodies; BMP, basic metabolic profile; BNP, B-type natriuretic peptide; CBC, complete blood count; CXR, chest x-ray; EF, ejection fraction; EKG, electrocardiogram; HF, heart failure; HIV, human immunodeficiency virus; LFTs, liver function tests; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TIBC, total iron binding capacity; TSH, thyroid stimulating hormone.

In this context, McMurray et al. now report in the Journal the primary results of the DAPA-HF randomized trial,4 in which they tested the hypoth-esis that dapagliflozin would reduce the primary composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardio-vascular death in patients with heart failure and a reduced ejection fraction, with or without type 2 diabetes mellitus. Among the patients who re-ceived dapagliflozin, the frequency of the pri-mary composite outcome was 26% lower than that among the patients who received placebo (386 [16.3%] and 502 [21.2%], respectively; haz-ard ratio, 0.74; 95% confidence interval, 0.65 to 0.85; P<0.001), with a number needed to treat of Multiple secondary cardiovascular outcomes were also positive, including a reduction in the total number of first and recurrent hospitaliza-tions for heart failure, a decrease in all-cause mortality, and an improvement in quality of life. There were many adjudicated events, and the benefits were remarkably consistent among out-comes and prespecified subgroups, which bolsters confidence in the conclusions. Dapagliflozin was associated with few adverse effects and with no excess of dangerous but rare adverse events, as was seen in some previous trials of SGLT2 inhibi-tors.1-3 In addition, hypoglycemia and volume depletion were uncommon.[8]

Other observations are worth highlighting. First, the benefit was additive to background therapies for heart failure, although the baseline systolic blood pressure and heart rate suggest-ed room for dose titration. Second, the magnitude of benefit was similar regardless of the presence or absence of type 2 diabetes. Third, the magnitude of benefit was similar to and reminiscent of the benefits of sacubitrilvalsartan, an angiotensin-receptor neprilysin inhibitor, in the PARADIGM-HF trial. Although the overall results of DAPA-HF are

compelling, several matters will require clarification. For example, almost all the patients had moderate heart failure, so the benefit and side-effect profile in patients with more severe heart failure will need further study. Furthermore, the background use of sacubitril–valsartan was limited (in approximately 10% of the patients), so definitive conclusions about the benefits and side effects associated with SGLT2 inhibition in combination with sacubitril–valsartan remain unclear.[9] Finally, data regarding the individual doses of background heart-failure therapies were not re-ported. Thus, the magnitude of benefit of SGLT2 inhibition might have been attenuated if the patients had been treated with higher doses of heart-failure medications. Multiple mechanisms for the benefit associated with dapagliflozin have and will be hypothesized6 but cannot be defined from this trial.

Nonetheless, the results are important and impressive, especially since they substantiate observations from previous trials of SGLT2 inhibitors. Will clinicians incorporate this new class of heart-failure medications into their daily practice? That remains to be seen, since there are barriers to the use of additional drugs in patients with heart failure, despite the evidence of benefit.7 Providers and patients are concerned about poly-pharmacy because of questions regarding the potential side effects of complex medical regi-mens, unanticipated drug interactions, and chal-lenges with adherence. Furthermore, administra-tive hurdles and the cost of new medications present additional difficulties. Paradoxically, these various issues may create a risk–treatment mis-match, in which patients at greatest risk are those least likely to receive appropriate treat-ment.8 Finally, medications that are used for the treatment of diabetes are complex and intimi-dating to many providers, particularly with the explosion of new drug classes for patients with diabetes and the multiple nuances to their use.[10]

In the end, it is not a question of having too many medications for heart-failure therapy but rather of using these drugs at doses that have been shown to be effective. It behooves us as clinicians to learn more about using such newer agents effectively, but we have a long way to go. In 2014, the PARADIGM-HF trial showed the benefits of a combination of sacubitril and val-sartan for heart failure with a reduced ejection fraction. In 2017, it was estimated that fewer than 15% of eligible patients were receiving that combination drug.9 Will we be waiting until 2022 before SGLT2 inhibitors are used in 15% of eligible patients with heart failure with a re-duced ejection fraction?

Keeping HF patients out of the hospital

Many readmissions to the hospital for HF exacerbation are preventable. Patients often do not understand hospital discharge instructions or the nature of their chronic disease and its management. [11] Routine follow-up in the office or clinic provides an opportunity to improve quality of life for patients and decrease admissions.

1. A major role for the family physician is in the co-creation of, and adherence to, an individualized, comprehensive care plan. Make sure such a plan is easily understood not only by the patient with HF, but also by his or her care team. In addition, it should be evidence-based and reflect the patient's culture, values, and goals of treatment. [15] At each visit, the family physician or a member of the health care team should assess adherence to guideline-directed medical therapy, measure weight, evaluate fluid status, and provide ongoing patient education including information on the importance of activity, monitoring weight daily, and moderating fluid, salt, and alcohol intake.

2. Research shows that cardiac rehabilitation improves functional capacity, exercise duration, quality of life, and mortality. Therefore, recommend it to all symptomatic patients with HF who are clinically stable.

3. Consider collaboration with a subspecialist. Patients who remain symptomatic despite optimal medical management and patients [16] with recurrent hospitalizations are best managed in conjunction with a subspecialist in HF treatment

Conclusions

In summary, the relationship between AF and HFrEF is clear. It is also apparent that, in many patients, AF causes symptomatic deterioration and may be associated with increased mortality. The difficulty is in identifying those patients in whom AF is simply a coexisting condition and those in whom AF is a major contributor to quality of life, ventricular function, and long-term mortality. Although clinical trials are no doubt the gold standard for evaluating treatments and strategies for treatment of AF in HFrEF patients, they can never fully address the need for an individualized approach. For patients who deteriorate early after the onset of AF despite adequate rate control, it is logical that an aggressive approach to rhythm control would be warranted. For those in whom the relationship between AF and symptoms of HF is less clear, a trial of sinus rhythm by performing cardioversion with or without concomitant antiarrhythmic therapy may help to assess whether the patient feels better and whether structural parameters like EF improve. For all patients, oral anticoagulation, lifestyle modifications, and

optimization of guideline-directed medical therapy are a must. Rate control should also be broadly applied, even if rhythm control is the final goal. Although RACE II has suggested that lenient rate control may be as good as stricter rate control, there were very few patients in that study with HFrEF and trials like AF-CHF used much stricter definitions of rate control.[12,] Therefore, guidelines continue to suggest that stricter rate control in HF patients, particularly those with reduced EF, is preferred.Finally, interventional approaches should be considered in HFrEF patients. Catheter ablation is an emerging and potentially promising therapy for HF patients in whom lasting rhythm control is desired. Ablation may reduce the morbidity associated with long-term treatment with antiarrhythmic agents such as amiodarone.[13,14] AV nodal ablation with resynchronization therapy should also not be overlooked, particularly for patients who may not be good candidates for catheter ablation (large left atrium, older age, multiple comorbidities) and in whom strict rate control may not be achieved through pharmacological treatment alone. With the imminent release of several clinical trial results in the near future, we can look forward to a further refinement in how we approach the treatment of patients with HF and concomitant AF.

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