Review Article

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New Advance in Heart Failure

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We are entering a new era for diagnosing and managing heart failure. The 2021 European Society of Cardiology established solid and evidenced based guidelines for diagnosis and treatment of heart failure; despite those, newer therapies and devices have met with great achievement. A careful review of recent literature remains essential for effective management of heart failure patients. (Roger, 2000; Jackon et al., 2000; Claggett et al., 2015).

In this minireview, we will discuss updates on definition, classification, symptoms, investigation, and management of heart failure. Most of the guidelines agreed on the definition of a clinical syndrome of heart failure as a heterogenous disease characterized by impairment of ventricular filling and/or ejection of blood to meet the requirements of the systemic circulation. This results in symptoms of organ hypoperfusion (such as tiredness, fatigue, and reduced exercise tolerance), and symptoms of pulmonary and systemic congestion (dyspnoea, paroxysmal nocturnal dyspnoea, orthopnoea, and bilateral ankle oedema). Cardinal signs are resting or inappropriate effort tachycardia, elevated jugular venous pressure, crackles over the back, pitting ankle oedema, third or fourth heart sound, summation gallop, pansystolic murmur over the lower left sternal border increasing with inspiration (suggestive of functional tricuspid incompetence), and congestive pulsatile hepatomegaly. Heart failure syndrome is due to structural and functional abnormalities of the heart leading to elevated intracardiac pressure, causing limitation of the cardiac output. Diagnosing the cause and type of heart failure is fundamental, as it guides the investigation, management and prognosis. (Jackon et al., 2000; Claggett et al., 2015; Wong et al., 2013).

Updated classification of heart failure based on echocardiophy are either:

- Heart failure with reduced ejection fraction less than 40%associated with symptoms and elevated BNP and ProBNP. (Wong et al., 2013).
- Hear failure with mild reduced ejection fraction (ejection fraction 41-49%).
- Heart failure with preserved ejection fraction (more than 50%).

Patients with high BMI who are difficult to diagnose by echocardiography due to poor acoustic window can be diagnosed by cardiac MR (CMR) with very high sensitivity and specificity. Although most heart failure is due to coronary artery disease, this should not discourage clinicians from investigating other causes, especially if the degree of coronary stenosis does not match with the severity of heart failure. Other causes of heart failure include uncontrolled hypertension, which can progress to malignant hypertension and acute cardiogenic oedema. Investigations to exclude secondary hypertension include renin and aldosterone, imaging for renal vessel to exclude fibromuscular hyperplasia and bilateral renal artery stenosis, and plasma metanephrines to exclude pheochromocytoma. Patients with episodic severe hypertension should be investigated for acute intermittent porphyria, pheochromocytoma and masked scleroderma crisis. 24-hour ambulatory blood pressure is important to confirm hypertension, especially in the absence of target organ damage. (Kemp & Conte, 2012; Ali et al., 1999).

Arrhythmia

Uncontrolled atrial and ventricular tachycardia can precipitate tachycardiomyopathy, a right arrhythmogenic cardiomyopathy due to fibrofatty replacement of the right ventricle and not uncommonly the left ventricle. This is a familial disorder. Genetic diagnosis is available; common mutations are TGFB3, TMEM43, PKP2, DSC2, DSG2 and PLN.

Cardiac MR and myocardial biopsy are diagnostic. Common clinical manifestations are cardiac syncope, palpitations, right heart failure, and sudden cardiac death. The disease has an impact on first-degree family members, and they should undergo counselling for genetic testing. Standard of care includes electrophysiologic study and ICD.

Patients diagnosed with heart failure due to uncontrolled atrial fibrillation or atrial flutter should be treated by beta blockers, digoxin, amiodarone, cardioversion, pulmonary vein isolation in paroxysmal AF, AV nodal ablation and pacemaker.

Valvular heart failure

With an aging population and improving diagnosis, aortic stenosis has become a common cause of heart failure in the elderly. It is characterised by low fixed cardiac output, which includes effort dyspnoea, chest pain and even cardiac syncope. Echocardiographic findings are left ventricular hypertrophy and left atrial enlargement. Auscultatory findings are a crescendo-decrescendo murmur over the aorta radiating to the carotid and occasionally to the mitral valve, making it difficult to rule out mitral incompetence.

Intensity of the murmur does not correspond with the severity of aortic stenosis. Late peaking of the murmur denotes decreased cardiac output and severe aortic stenosis. In critical aortic stenosis there may be paradoxical splitting of the second heart sound, or it may even be either muffled or absent. Patients with a bicuspid aortic valve usually develop an aortic systolic click. The apical impulse will not be displaced until the patient has developed left ventricular dilation. Echocardiography can assess the anatomy of the valve, including whether it is trileaflet or bicuspid, sclerotic or thickened. In addition to reduced aortic valve area, doppler study can access the severity of aortic stenosis with the aortic jet velocity. In patients with low cardiac output due to left ventricular dysfunction, elevated gradient across the aortic valve and reduced aortic valve area do not correspond with the severity of aortic stenosis. Patients with low flow gradient should have a dobutamine study to assess if they have a flow reserve and will benefit from transcatheter aortic valve implantation (TAVI). Patients with concomitant ischemic heart disease should have coronary angiography if they are suitable for coronary artery bypass grafting (CABG). (Ali et al., 1999; Mc Murray et al., 2005; Habal et al., 2017; king et al., 2012).

Patients with asymptomatic aortic incompetence should be treated with a vasodilator.

Patients with early decrease in ejection fraction should have aortic valve replacement even before developing symptoms of heart failure.

Patients with primary mitral incompetence and heart failure should be treated with early mitral repair. Secondary mitral incompetence due to left ventricular failure and mitral annulus enlargement due to left atrial enlargement should be referred to a multidisciplinary team including a heart failure specialist and cardiac surgeon.

Patients with heart failure and tricuspid regurgitation should be referred to a surgeon if the tricuspid regurgitation requires left sided surgery.

Cardiomyopathy

All patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or arrhythmogenic cardiomyopathy need right and left heart catheterisation. Patients with Takotsubo syndrome need to be investigated with coronary angiography and cardiac MR.

Cardiac MR has a very high specificity to differentiate ischaemic cardiomyopathy from non-ischaemic cardiomyopathy. Ischaemic cardiomyopathy is characterised by late gadolinium enhancement in the subendocardium and transmurally, and it also follows a vascular distribution of impaired coronary circulation. Non-ischaemic cardiomyopathy is characterised by late gadolinium enhancement in the mid-wall or epicardium and does not correspond to a particular coronary artery distribution. CMR has very high sensitivity and specificity (close to 100%) in diagnosing noncompaction left ventricular cardiomyopathy. Early myocarditis can be diagnosed with CMR, with specific findings including myocardial oedema and patchy myocardial late gadolinium enhancement. Tissue oedema is best visualized in T2-weighted spin-echo CMR. Takotsubo cardiomyopathy can be diagnosed with high sensitivity and specificity by CMR. Cardinal features include apical ballooning, absent gadolinium enhancement and wall motion abnormalities.

Congenital Heart Diseases

Atrial septal defect, ventricular septal defect, patent ductus arteriosus, transposition of the great vessels, repaired tetralogy of Fallot, and Epstein's anomaly can all cause heart failure and Eisenmenger Syndrome. Haemodynamically significant patent ductus arteriosus can cause heart failure if patients develop any degree of pulmonary hypertension. Cardiac MR and right heart catheterisation are the standard of care.

Patients should be referred to a specialist heart centre with a high volume of management of congenital heart disease.

Endomyocardial Disease

Eosinophilic myocarditis should be diagnosed by myocardial biopsy because of the availability of curative treatment in the form of steroid and immunosuppressive medication.

Patients with history of radiotherapy should be investigated with cardiac MR.

Patients with carcinoid should be investigated with serum chromogranin, 24 hours 5 hydroxyindoleacetic acid (5-HIAA), octreotide scan, and PET-scan.

Pericardial Disease

Patients with pericardial disease should be investigated with right and left heart catheter and CMR. Constrictive pericarditis is curable if it is autoimmune, as it can be medically treated. Other forms of severe constrictive pericarditis due to chronic infection like tuberculosis can be treated surgically. Differentiating restrictive cardiomyopathy versus constrictive cardiomyopathy remains difficult even with haemodynamic studies, and endomyocardial biopsy is needed to avoid unnecessary cardiac surgery.

Metabolic Cardiomyopathy

These include pheochromocytoma, Cushing syndrome, thyrotoxicosis, Paget disease of bone, hyperaldosteronism, hyperparathyroidism, and acromegaly. Patients should be investigated with thyroid function, serum calcium, phosphate,

parathyroid immune assay, insulin growth factor, renin and aldosterone, serum metanephrines, alkaline phosphatase, urinary hydroxyproline and HbA_1c.

Nutritional Cardiomyopathy

Investigations should include vitamin C assay, B1, B7, selenium, iron, ferritin, transferrin saturation, thiamine, Vitamin B7, DM, deficiency of coenzyme Q10, vitamin D, creatine, and amino acids (taurine, carnitine, arginine, carnosine).

Autoimmune Cardiomyopathy

Tests should include vasculitis and autoimmune screening to exclude RA, scleroderma, mixed connective tissue disease, and SLE.

Neuromuscular Cardiomyopathy

These include Duchenne muscular dystrophy, myotonia dystrophica, Friedreich ataxia, limb girdle muscular dystrophy, fascioscapulohumeral muscular dystrophy, and mitochondrial muscular dystrophy.

Patients should be investigated with nerve conduction studies, EMG, CK, lactate, and genetics. They should be cared for by a multidisciplinary team including a muscular dystrophy specialist, heart failure specialist, genetic specialist with an interest in genetic heart failure, and mitochondrial disease allied health.

Storage Disease Cardiomyopathy

Cardiac Haemochromatosis

These should be investigated with iron studies, cardiac MRI, and genetics.

Cardiac MRI T2 image is highly sensitive in diagnosing myocardial iron deposition. Early diagnosis is fundamental as cure is possible if patients are treated in a timely manner.

Fabry Disease

Investigations should include alpha galactosidase A, genetics, echocardiography, and CMR. CMR is sensitive and specific for confirming the diagnosis, and will show late gadolinium enhancement within the mid-wall and posterolateral basal segments associated with decreased regional functioning by strain and strain-rate imaging.

Diastolic dysfunction is the most common feature of the disease.

Common findings in echocardiography are:

- Left ventricular mass index is more than 95g/m in females and more than 115g/m in males.
- Relative wall thickness more than 0.42
- Left atrium volume index more than 34ml/m in sinus rhythm and more than 40 in AF
- Early filling mitral velocity on transmittal doppler/early relaxation velocity on tissue Doppler is more. < 9
- E/e on exercise >15
- Tricuspid regurge Velocity at peak stress >3.4m./s
- Left ventricular global strain <16%
- Pulmonary capillary wedge pressure >15 at rest and >25 on exercise,
- Left ventricular end diastolic pressure >16 mm hg
- Pulmonary artery systolic pressure >35mmhg at rest
- Tricuspid peak velocity at rest >2.8m/S

Glycogen Storage Disease (Danon Disease)

Danon disease is a rare genetic cardiomyopathy characterised by left ventricular hypertrophy in the absence of hypertension, aortic stenosis, or hypertrophic cardiomyopathy. The two common mutations causing cardiomyopathy are LAMP2 and PRKAG2.

It is an autosomal recessive disease in which deficiency of glycogen branching enzyme leads to accumulation of abnormal glycogen in the myocardium and other tissue in the body.

Infiltrative Cardiomyopathy

Cardiac Amyloidosis

The two most common types of cardiac amyloids are light chain amyloidosis and familial amyloidosis.

Light chain amyloidosis (AL) is caused by plasma cell dyscrasia leading to deposition of misfolded immunoglobulin light chain extracellularly throughout the heart and other organs. Early cardiac amyloidosis is a major diagnostic challenge. Peripheral neuropathy and autonomic neuropathy are common manifestations secondary to cardiac amyloidosis. Other findings supporting the diagnosis of AL amyloidosis are macroglossia, periorbital bruising, low voltage ECG, AV conduction disease, renal insufficiency, and proteinuria.

Cardiac MR is characteristic for subendocardial late gadolinium enhancement, elevated native T1 values, increased extracellular volume and abnormal gadolinium kinetics.

Transthyretin Amyloidosis (ATTR)

Wild type transthyretin amyloidosis is a non-hereditary transthyretin-related amyloidosis, formally called senile amyloidosis. It usually occurs after the seventh decade and is mostly underdiagnosed. Tc-DPD scintigraphy is diagnostic.

Hereditary Transthyretin Amyloidosis

The most common mutations are Va30Met, TH60Ala, Ser77Tyr and VaLL22LLe. Correlation between genotype and clinical manifestation is strong for certain mutations.

All diagnoses of amyloidosis need histological confirmation of amyloid deposition, with misfolded extracellular amyloid fibres which stain positive for Congo red. ATTR amyloidosis is characterised by specific clinical manifestations such as bilateral carpel tunnel syndrome, renal insufficiency, proteinuria, vitreous deposits, lumbar spinal stenosis, ruptured biceps tendon, deafness, and strong family history.

Liver transplant is curative if the disease is diagnosed and treated in a timely manner before irreversible cardiac damage.

Sarcoid Cardiomyopathy

This is a very difficult diagnosis to be made; there is no specific pathologic or image marker which can diagnose sarcoidosis, and even histological diagnosis is not 100% accurate as many diseases can be histologically the same. Non-caseating granuloma can occur with infection, inflammation, drugs and not uncommonly malignancy and degenerative diseases.

Cardiac MRI findings include increased intramyocardial signal intensity on T2-weighted images from oedema and granuloma. The pattern of enhancement is due to increased signal in the mid portion of myocardium and epicardium and not in the endocardium. Normalisation of the enhancement after steroid therapy is supportive of the diagnosis.

Toxic Cardiomyopathy

Drugs which cause toxic cardiomyopathy included anthracycline, 5-fluorouracil, trastuzumab, immune check point inhibitors, protein kinase inhibitors, vascular endothelial growth factor inhibitor (VEGF) and proteasome inhibitors.

Guidelines advise that patients should have a baseline echocardiogram, BNP, and troponin before starting on these medications, and should be followed up by an oncologist with an interest in cardiomyopathy. If patients develop heart failure, they should be treated in the pathway of heart failure in consultation with a cardiologist with an interest in oncology.

Infective Cardiomyopathy

The cardiotropic viruses causing myocarditis and cardiomyopathy include adenovirus, enterovirus, human herpes 6 virus, parvovirus 19, Epstein - Barr virus, cytomegalovirus, hepatitis B, HIV, influenza virus, mumps virus, respiratory syncytial virus, and rubella virus.

Few bacteria can cause myocarditis. These include but are not limited to brucellosis, diphtheria, clostridia, legionella, mycoplasma, pneumococcus, haemophilus, streptococcus, staphylococcus, and tropheryma.

Fungal infections causing myocarditis include actinomycosis, aspergillus, blastomycosis, candida, and histoplasma.

Other infections causing myocarditis include Rickettsial infections (Rocky Mountain spotted fever, Q fever, and typhus), spirochetal infections (syphilis, leptospirosis, and borrelia), and *Trypanosoma cruzi*(causing Chagas disease). Diagnosis can be confirmed by septic screen, serology, and cardiac biopsy.

Recent Trend in Investigating Heart Failure

(Habal & Garan, 2017; king et al., 2012; Lind et al., 2021; Reddy et al., 2016).

Cardiac MR is the standard of care to distinguish non ischaemic and ischaemic cardiomyopathy.

All patients with constrictive, restrictive, infiltrative, metabolic, and genetic cardiomyopathy should have cardiac MR. CT coronary angiography should be for every patient with a low probability of ischaemic heart disease.

Cardiopulmonary exercise testing and right heart catheter is part of the work up for patients with pulmonary hypertension or those receiving a heart transplant.

Acute Heart Failure

Patients with acute heart failure could be one of the following.

- Acute decompensated heart failure
- Acute pulmonary oedema
- Cardiogenic shock.

Management in 2022

Management includes oxygen therapy if the saturation is ≤90% or PaO_2<60. Non-hypoxic patients should not be offered oxygen, as it causes coronary vasoconstriction, hypotension and increases ventilation-perfusion mismatch.

If respiratory rate is >25/min and the patient is hypoxic, positive pressure non-invasive ventilation should be started without delay as a treatment or bridge to intubation and mechanical ventilation unless contraindicated.

Diuretics (Reddy et al., 2016; Lesyuk et al., 2018).

Intravenous loop diuretics should be started immediately in patients with congestion; furosemide is the preferred drug due to rapid onset of action. Daily single dosing is discouraged as it can cause post- dosing salt and water retention.

Diuretic effect should be evaluated by measuring sodium in a spot urine after 2 hours; sodium less than 50 meq/L and urine output less than 100ml/h denotes inefficiency or diuretic resistance. In this case, the loop diuretic dose should be doubled and another diuretic with a different mechanism of action should be added, such as thiazide, acetazolamide, metolazone, or mineralocorticoid blockers. This should be followed by repeated electrolytes and kidney function. Changing to oral medication should happen after treating the congestion. (Lesyuk et al., 2018; Heidenreich et al., 2022)

Vasodilators

Patients with ischemic chest pain and systolic blood pressure >110mmHg should start on isosorbide mononitrates to lower the afterload and increase stroke volume. Patients who need nitrates and have a low blood pressure should start on inotropes; usually those patients have hypotension and low cardiac output. Patients on beta blockers should avoid inotropes with adrenergic mechanisms and use a type-3 phosphodiesterase inhibitor instead. Opiates should not be used except for severe anxiety, for example in patients started on non-invasive ventilation. (Butler et al., 2022; Jones et al., 2019; Seferovic et al., 2021).

Digoxin can be used in patients with AF in sinus rhythm if beta blockers did not control the ventricular rate. Patients who develop AF due to heart failure have the worst prognosis and management should concentrate on treatment of congestion.

Patients who have tachycardiomyopathy due to AF should receive treatment mainly to control AF, and thromboprophylaxis should offered to all patients. Patients who do not improve or develop cardiogenic shock will need short term mechanical circulatory support. (Seferovic et al., 2021; Tomasoni et al., 2020; Groenewegen et al., 2020).

Intra-aortic balloon pump (IABP) is used for patients with cardiogenic shock if they do not improve with diuretics, vasodilators, inotropes, and vasopressors. If acute coronary syndrome has been ruled out, severe cardiogenic shock can be treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO) as ECMO can increase the after load and pulmonary congestion. Transseptal ventricular apex vent may help to de-load the left ventricle. VA-ECMO can only work as a salvage and bridge to more durable mechanical support like left ventricular assist device. During VA-ECMO treatment, left ventricular unloading can be achieved by inotropes, vasodilators, IABP, balloon atrial septostomy, left atrium to aorta cannula connected to the venous part of ECMO circuit, surgical left ventricular vent, percutaneous left ventricular vent, impella, and lastly offpump central VA-ECMO.

Reversible e causes of acute heart failure

(Mc Murray et al., 2014; NICE, 2016; Conrad et al., 2018; Moss et al., 2002; Hayashi et al., 2015).

- Acute coronary syndrome
- Accelerated malignant hypertension
- Systemic sclerosis renal crisis
- Acute intermittent porphyria
- Severe autonomic hypertension due to Guillain-Barre syndrome, drugs like cocaine, NMDA
- Pheochromocytoma
- Bilateral renal artery stenosis
- Posterior reversible leukoencephalopathy
- Reversible vasoconstrictor syndrome
- Acute lead poisoning
- Peripartum cardiomyopathy
- Acute viral myocarditis
- Infective endocarditis
- Acute mitral regurgitation
- Acute papillary muscular dysfunction
- Acute ventricular septal defect
- Acute mechanical heart failure
- Acute high output heart failure
- Takotsubo syndrome
- Tachycardiomyopathy
- Alcohol-induced cardiomyopathy
- Acute metabolic heart failure due to B1 and B7 deficiency
- Acute right ventricular failure due to massive pulmonary embolism
- Right ventricular arrhythmogenic cardiomyopathy
- Toxic drug induced cardiomyopathy
- Acute pulmonary hypertension due to massive pulmonary hypertension in patients with reduced cardiac reserve
- Chronic heart failure with reduced ejection fraction (<40%)
- Chronic heart failure with mildly reduced ejection fraction (40-49%)
- Chronic heart failure with preserved ejection fraction (50% and above)

Heart failure with reduced ejection fraction, prior heart failure and mildly reduced ejection fraction are treated the same. Patients with reduced ejection fraction who improve with increase in ejection fraction should not stop medications. The same applies for patients with heart failure and preserved ejection fraction.

All patients with chronic heart failure should be managed by a multidisciplinary team in heart failure clinic. They should have the following work up:

- FBC, urea electrolytes, Mg. Phosphate, iron study, thyroid function, PNB and ProPNB, ESR, calcium, LFT, ACR from urine.
- Echo with contract to exclude cardiac shunt in patient with chronic liver disease.
- Cardiac MR when differential diagnosis included myocarditis, infiltrative cardiomyopathy (Hemochromatosis, amyloidosis, Fabry disease, non-ischemic cardiomyopathy, non-compaction cardiomyopathy.
- Coronary Angio for patients with suspected IHD,
- Exercise testing to exclude reversible ischemia, nuclear scan and exercise echo for patient who can't exercise. (Lane et al., 2005; Mann et al., 1999; Aurcchio et al., 1999; Saxon et al., 2002).
- CT coronary for patients with low probability ischemic heart disease.

Patients considered for coronary revascularisation may be considered for PET and SPECT. Cardiopulmonary exercise and right heart catheterisation should be considered for patients having cardiac transplant or mechanical circulatory support. All patients suspected to have constrictive pericarditis, restrictive pericarditis, congenital heart disease or high output heart failure should have right heart catheterisation. Patients with heart failure with preserved ejection fraction may be candidates for right heart catheterisation to exclude alternative diagnosis.

Patients with no diagnosis or no response to standard treatment should have endomyocardial biopsy. Patients with suspected eosinophilic myocarditis or transthyretin hereditary cardiomyopathy should have endomyocardial biopsy.

Pharmacotherapy for patient with chronic heart failure with reduced ejection fraction and mildly reduced ejection fraction. (Gras et al., 2002; Leclercq et al., 2002; Cleland et al., 2001).

Patients with symptomatic congestion should be treated in the hospital with intravenous loop diuretics, with sodium measured in urine after 6 hours to rule out diuretic resistance (sodium less than 50 meq/L). Patients with no response or who have

developed resistance should receive double the dose of loop diuretics and/or have another diuretic added, such as thiazide or acetazolamide. Single doses of diuretics should be avoided to prevent sodium and water retention.

The pathogenesis of heart failure is activation of renin,angiotensin, aldosterone, sympathetic, vasopressin system causing sodium and water retention.

Non-selective beta blockers and mineralocorticoid receptor inhibitors (MRA) are the cornerstone of pharmacotherapy and act to increase survival and improve quality of life. All medications should be titrated to doses used in the clinical trials or the maximum doses tolerated by the patients.

Indication of angiotensin receptor-neprilysin inhibitor (ARINI)

Most of the guidelines support starting ARINI in patients with symptomatic heart failure in ACE-I naïve patients or by replacing a prior ACE-I after a 36 hour wash out. All patients should have estimated GFR >30ml/min/1.73m. ARINI is very well tolerated with less hyperkalaemia and may facilitate reduction of the loop diuretic dose.

Patients can develop symptomatic hypotension but will still receive all the clinical benefits of the drug. The starting dose of ARINI is 24/26 mg BID to be increased gradually every two weeks, with a maximum dose of 97/103mg BD. All patients with heart failure with reduced ejection fraction should be started on sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) regardless of whether they have diabetes or not, as it reduces all-cause mortality, improves symptoms, and improves kidney function. Dapagliflozin is preferred over empagliflozin. (Leon et al., 2002; Reuter et al., 2002).

Patients who cannot tolerate ARINI and ACE-I should start on ARB or selective beta blockers. Guidelines did not advise on which drug should be started first, but it is the authors' opinion that we start on beta blockers first for patients with tachycardia or hypotension, that we try to avoid carvedilol for patients with hypotension due to the vasodilating effect, and that in the absence of hypotension we start on ACE-I or ARB.

We do not stop or reduce the dose of beta blocker for patients on beta blockers who develop decompensation of heart failure causing congestion.

Patients who are still symptomatic after receiving the maximum doses of ACE-I, ARB, beta blockers, ARINI and mineralocorticoid inhibitor, have a resting heart rate >70/min and are in sinus rhythm should be started on ivabradine.

Patients who cannot tolerate beta blockers should also receive ivabradine. Patients with symptomatic heart failure NYHA class II-III should be started on vericiguat (soluble guanylate receptor stimulator). Hydralazine and isosorbide dinitrate should be considered for patients with reduced ejection fraction, a dilated left ventricle despite having been on ACE-I or ARB or ARINI and beta blocker, and NYHA class III-IV. Black patients are commonly resistant to standard of care heart failure medications.

Digoxin may be considered in symptomatic patients with heart failure with reduced ejection fraction despite maximum doses of standard pharmacotherapy even if they are in sinus rhythm, as it reduces the risk of hospitalisation.

Cardiac rhythm management in heart failure with reduced ejection fraction

Implantable cardioverter defibrillators (ICD)

ICD is indicated as a secondary prevention to reduce the risk of sudden death in patients who sustained recovery from arrhythmogenic death and are expected to live more than one year, except if ventricular arrhythmia occurred less than 48 hours ago in the context of myocardial infarction.

ICD is indicated as a primary prevention to reduce the risk of arrhythmogenic cardiac death in symptomatic patients with NYHA class II-III due to ischemic heart failure and ejection fraction less than 35% despite maximal medical therapy if patient has not had a heart attack in the last 40 days.

ICD should be considered for patients with NYHA II-III of non-ischemic aetiology if the patient had ejection fraction less than 35% despite three months of optimum medical therapy.

ICD is not indicated in patients with NYHA class IV unless the patient is a candidate for CRT, ventricular assist device (VAD) or cardiac transplant.

ICD is not indicated in the first 40 days after myocardial infarction.

Wearable ICD can be considered as a bridge to implantable ICD.

Cardiac Resynchronization Treatment

CRT is indicated for symptomatic heart failure patients in sinus rhythm with QRS duration >150ms, left bundle branch pattern QRS morphology, or with left ventricular ejection fraction less than 35% despite optimum medical therapy, as it improves symptoms, morbidity, and mortality.

CRT is indicated to reduce morbidity in patients with high degree AV block, regardless of symptoms or QRS duration or morphology. This includes patients with atrial fibrillation. ICD is indicated in symptomatic patients with heart failure and left ventricular ejection fraction less than 35% who are in sinus rhythm with QRS 130-149 and LBBB morphology and are receiving maximal medical therapy with no improvement.

CRT is indicated in symptomatic patients with heart failure, ejection fraction <35% despite maximum medical therapy, and QRS duration more than 150ms regardless of QRS morphology. CRT is indicated in symptomatic patients with ejection fraction less than 35% despite ICD and maximum right ventricular pacing and medical therapy. Patients who received CRT may require lower doses of diuretics and maximal therapy.

Few observational studies reported that the benefits of CRT decline when biventricular capture is less than 98%. This could be due to loss of resynchronisation, which could be fixed by device programming. Again, it could be due to increased burden of scars in the myocardium or poor placement of the left ventricular leads. (Reuter et al., 2002; Garrigue et al., 2001; Yancy et al., 2013).

Management of Cardiovascular Comorbidities

Atrial Fibrillation

Atrial fibrillation can precipitate acute decompensated heart failure with congestion in patients with chronic heart failure, through mechanisms such as cardiac remodelling, activation of RAAS system, and tachycardia-induced heart failure. This phenotype of patients has a better prognosis than patients who develop AF due to chronic heart failure. Identification of triggers for AF is important, with common causes being electrolyte disturbance, cessation of medication, hyperthyroidism, infection, and alcohol binge. Notably, the presence of AF may reduce the benefit of beta blockers and ivabradine.

Treating congestion and reducing ventricular rate may increase the chance to return to sinus rhythm.

Drugs which can convert AF to sinus rhythm include amiodarone, sotalol and flecainide. Amiodarone has few side effects if used long-term to maintain sinus rhythm. Sotalol can increase Q-T interval and may be proarrhythmic. Flecainide is contraindicated in structural heart disease as it increases mortality.

All patients with AF (whether paroxysmal, permanent, or chronic), heart failure and CHA2DS2-VASc score of either 1 in men or 2 in women should start on non-vitamin K antagonists. The exception is patients with mild to severe mitral stenosis and mechanical valve, who should be on warfarin. Patients with AF and heart failure should initially be treated for rhythm control with isolation of pulmonary veins in paroxysmal AF.

Catheter ablation for rhythm control was tried with some success. Patients who did not achieve rate control despite beta blocker, digoxin and amiodarone should have AV node ablation and pacemaker.

Patients who could not tolerate anticoagulation should have left atrial appendage closure (best practise and not included in the guidelines).

Thyroid Disease

All patients under 70 years with TSH>10miul/L and normal T4 and T3 should be treated for subclinical hypothyroidism, especially if TSH receptor antibody are positive. Both hypothyroidism and hyperthyroidism can cause AF and should be treated.

Iron Deficiency Anemia and Functional Iron Deficiency

All patients with heart failure, serum ferritin<100ng/ml or 100-299ng/ml and transferrin saturation 20% should receive an iron infusion if they do not have active infection. Kidney dysfunction with an increase in serum creatinine less than 50% above baseline after initiation of ACE-I, ARB, mineralocorticoid blockers, or ARINI is not an indication to withhold medication. Continuation of such medication with transient kidney dysfunction gives more benefit than in patients with normal kidney function. There is no evidence to support the current strategy in severe kidney dysfunction.

Patients with heart failure get improvement in cardiac output and kidney function after CRT or left ventricular assist device. Hypochloraemia and hyponatraemia are poor prognostic markers of heart failure. Severe hyponatremia in advanced heart failure due to hypersecretion of vasopressin can be treated with hypertonic saline and loop diuretics. Tolvaptan (selective vasopressin V2 inhibitor) showed promising results in a few studies, but it did not reduce mortality.

Sleep Disordered Breathing

Sleep disordered breathing could be central sleep apnoea or obstructive sleep apnoea. Positive pressure airway mask is contraindicated in central sleep apnoea, but implantable phrenic nerve stimulation can relieve symptoms. CPAP or bilevel positive air way pressure can treat nocturnal hypoxaemia in obstructive sleep apnoea, which can help in hypoxemic pulmonary hypertension and heart failure. It could also treat hypertension to an extent that patient might not need to continue antihypertensive medication.

Hyperlipidemia

Based on updated research, statins are not indicated in heart failure. However, patients who are on statins for IHD should continue statin therapy.

Gout and Hyperuricemia

All-cause mortality and morbidity increase with hyperuricaemia. Allopurinol and febuxostat are recommended for treating hyperuricemia in patients with chronic heart failure.

Erectile Dysfunction

Erectile dysfunction occurs in patients with heart failure due to diabetes, beta blockers or even diuretics. Phosphodiesterase type-5 inhibitors are safe to use in compensated heart failure; it is a novel therapeutic strategy for overexpressing NO signalling by increasing cGMP availability with additive benefit in heart failure patients.

Malignancy

Patients with heart failure and cardiomyopathy are at risk to decompensate with cardiotoxic immunosuppressive medication. Careful cardiovascular risk assessment should take place by a cardiologist with an interest in malignancy. (Ho et al., 1993; Boyle, 2021; Tsukui et al., 2007; Feldman et al., 2013; Strueber et al., 2010; Jakovlljevic et al., 2017).

Heart Failure with Preserved Ejection Fraction

Despite the progress in diagnosing and management in heart failure with reduced ejection fraction, no medical therapy has demonstrated reduction in all-cause mortality or cardiovascular death in heart failure with preserved ejection fraction. Treatment of heart failure with preserved ejection fraction stems mainly from treating comorbidities, such as ischemic heart disease, hypertension, diabetes mellitus, aortic stenosis, and obesity. (Gasparini et al., 2008; Steffel et al., 2014; Packer et al., 2001; Bleeker et al., 2006; Leyva et al., 2011; Bennets et al., 2021).

RAAS inhibitors, ARINI, SGLT2 inhibitors and beta blockers continue to reduce hospitalisation and reduce symptoms, but do not reduce mortality and cardiac death. At the time of editing this article, SGLT2 inhibitors had received approval in European societies for heart failure with preserved ejection fraction as they showed a positive impact on cardiac mortality. Most European guidelines eliminate high ProBNP as a required criteria to diagnose heart failure with preserved ejection fraction due to the high sensitivity and low specificity for this cohort of old patient with comorbidities.

Conclusion

Heart failure is a complex syndrome with debilitated symptoms and leading cause of hospitalization and death all over the world, the emergence of new medication such as RAAS, Sinoatrial modulation with Ivabradine, titrating beta blocker to the maximum dose tolerated, ARINI, SGL2 inhibitor consideration of resynchronization for appropriate patient, treating comorbidity, close monitoring of patient with heart failure multidisciplinary team, introducing Diflunisal for patient with Transthyretin cardiomyopathy.

Treating iron deficiency anemia and functional iron deficiency with carboxymaltose, involving palliative care early had slowed the progression of the disease, reduced death and health care costs, improved the quality of life, reduced multiple admissions due to decomnsated heart failure and reduced mortality. (Mack et al., 2019; Meredith et al., 2015; Quine et al., 2020; Lung et al., 2005).

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