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CONGESTIVE HEART FAILURE: A REVIEW

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ABSTRACT

Despite the advancement in medicine, management of heart failure (HF), which usually presents as a disease syndrome, has been a challenge to healthcare providers. This is reflected by the relatively higher rate of readmissions along with increased mortality and morbidity associated with HF. In this review article, we first provide a general overview of types of HF pathogenesis and diagnostic features of HF including the crucial role of exercise in determining the severity of heart failure, the efficacy of therapeutic strategies and the morbidity/mortality of HF. We then discuss the quality control measures to prevent the growing readmission rates for HF. We also attempt to elucidate published and ongoing clinical trials for HF in an effort to evaluate the standard and novel therapeutic approaches, including stem cell and gene therapies, to reduce the morbidity and mortality. Finally, we discuss the appropriate utilization/documentation and medical coding based on the severity of the HF alone and with minor and major co-morbidities. We consider that this review provides an extensive overview of the HF in terms of disease pathophysiology, management and documentation for the general readers, as well as for the clinicians/physicians/hospitalist. Integrated system can regulate drug release, receive sensor feedback and transmit updates

INTRODUCTION

Heart failure is a common and complex clinical syndrome that results from any functional or structural heart disorder, impairing ventricular filling or ejection of blood to the systemic circulation to meet the body's needs. Heart failure can be caused by diseases of the endocardium, myocardium, pericardium, heart valves, vessels or metabolic disorders. Most patients with Heart failure have symptoms due to impaired left ventricular myocardial function. Patients usually present with dyspnea and fatigue limiting exercise tolerance, fluid retention characterized by pulmonary and peripheral edema. Heart failure due to left ventricular dysfunction is categorized according to left ventricular ejection fraction (LVEF) into heart failure with reduced ejection fraction (LVEF 40% or less), known as HFrEF and heart failure with preserved ejection fraction (LVEF greater than 40%); known as HFpEF.

Heart failure does not mean the heart has topped working. Rather, it means that the heart works less efficiently than normal. Due to various possible causes, blood moves through the heart and body at a slower rate, and pressure in the heart increases. As a result, the heart cannot pump enough oxygen and nutrients to meet the body's needs. The chambers of the heart may respond by stretching to hold more blood to pump through the body or by becoming stiff and thickened. This helps to keep the blood moving, but the heart muscle walls may eventually weaken and become unable to pump as efficiently. AS a result, the kidneys may respond by causing the body to retain fluid (water) and salt. If fluid builds up in the arms, legs, ankles, feet, lungs, or other organs, the body becomes congested, and congestive heart failure is the term used to describe the condition. Based on LVEF, heart failure is defined as follows;

1. Heart failure with reduced ejection fraction (HFrEF): symptoms and signs with LVEF<40%.

2. Heart failure with mid-range ejection fraction (HFrEF): symptoms and signs with LVEF 40% to 49%. Other features include elevated natriuretic peptides (B-type natriuretic peptide [BNP] >35 picograms/mL or N-terminal pro-brain natriuretic peptide [NT-pro-BNP] >125 picograms/mL) and at least one additional criterion: (a) relevant structural heart diseases (e.g., left ventricular hypertrophy [LVH] or left atrial enlargement), (b) diastolic dysfunction.

3. Heart failure with preserved ejection fraction (HF-pEF): symptoms and sings with LVEF>50%. Other features include elevated natriuretic peptides (BNP >35

picograms/mL or NT-pro-BNP >125 picograms/mL) and at least one additional criteria: (a) relevant structural heart disease (e.g., LVH or left atrial enlargement), (b) diastolic dysfunction. Keywords: bnp, congestive heart failure, natriuretic peptide, nesiritide.

CLASSIFICATION

Heart failure can be classified as predominantly left ventricular, right ventricular or biventricular based on the location of the deficit. Depending on the time of onset, HF is classified as acute or chronic. Clinically, it is typically classified into two major types based on the functional status of heart: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF. In patients with HFpEF who are mostly females and older adults, EF is usually more than 50%; the volume of the left-ventricular (LV) cavity is typically normal, but the LV wall is thickened and stiff; hence, the ratio of LV mass/end-diastolic volume is high. HFpEF is further categorized as borderline HF if the EF stays between 41% and 49% and improved HF if EF is more than 40%. In contrast, in patients with HFrEF, the LV cavity is typically dilated, and the ratio of LV mass/end-diastolic volume is either normal or reduced. At the cellular level, both cardiomyocyte diameter and the volume of myofibrils are higher in HFpEF than in Free. As far as treatment and outcome are concerned, patients with HFrEF respond favorably to the standard pharmacological treatment regimen and demonstrate better prognosis. In contrast, patients with HFpEF have not been shown to respond to standard pharmacological treatments, except for nitrates, and therefore, have a poor prognosis, especially during the decompensated phase of HF. In addition, based on cardiac output, HF is also classified as high-output failure and low-output failure. High-output failure is an uncommon disorder characterized by an elevated resting cardiac index of greater than 2.5-4.0 L/min/m2 and low systemic vascular resistance. The common causes of high output failure are severe anemia, vascular shunting, hyperthyroidism and vitamin B1 deficiency. This occurs as a result of ineffective blood volume and pressure, which stimulate the sympathetic nervous system and rennin-angiotensin-aldosterone system (RAAS), causing the release of antidiuretic hormone (ADZ), which all together ultimately lead to ventricular enlargement, negative ventricular remodelling and HF. Low output failure is much more common than high-output failure and is characterized by insufficient forward cardiac output, particularly during times of increased metabolic demand. Left ventricular dysfunction due to large MI, right ventricular dysfunction

due to an acute pulmonary embolus and biventricular dysfunction are important causes of low output failure. More recently, exercise intolerance in HFpEF is proposed to be due to a decrease in oxygen delivery to or impaired oxygen utilization by the exercising skeletal muscles. Oxygen utilization is being calculated as the arterial- venous oxygen content difference (A-VO2Diff), rather than reduced cardiac output (CO). Considering the slowed down oxygen uptake kinetics in HF along with peripheral muscle function impairment, exercise rehabilitation seems to be a logical and essential factor in improving the inflammatory imbalance, relieving elevated cardiac filling pressures, restoring exercise capacity, quality of life and reducing morbidity and mortality associated with HF. Hence, exercise training, mostly high intensity as opposed to moderate, in HFpEF patients has been significantly shown to improve rate of oxygen consumption or VO2 without affecting endothelial function.

The New York Heart Association (NYHA) functional Classification defines four functional classes

NYHA Class   Patients with Cardiac Disease (Description of HF Related Symptoms)

Class I (Mind): Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heartbeat), dyspnea (shortness of breath), or anginal pain (chest pain).

Class II (Mild)Patients with cardiac disease resulting in slight limitation of physical activity they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain

Class III (Moderate): Patients with cardiac disease resulting in marked limitation of physical activity they are comfortable at rest. Less than ordinary activity causes fatigue, palpitation dyspnea, or anginal pain.

Class IV (Severe):   Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Types of Congestive Heart Failure:-

Systolic Dysfunction: - Systolic dysfunction (or systolic heart failure) occurs when the heart muscle doesn't contract with enough force, so there is less oxygen-rich blood that is pumped throughout the body. Heart failure caused by systolic dysfunction is more readily recognized.

It can be simplistically described as a failure of the pump function of the heart. It is characterized by a decreased ejection fraction (less than 45%). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components. In congential diseases such as Duchenne muscular dystrophy, the molecular structure of individual myocytes is affected. Myocytes and their components can be damaged by inflammation (such as in myocarditis) or by infiltration (such as in amyloidosis). Toxins and pharmacological agents (such as ethanol, cocaine, doxorubicin, and amphetamines) cause intracellular damage and oxidative stress. The most common mechanism of damage is ischemia causing infarction and scar formation. After myocardial infarction, dead myocytes are replaced by scar tissue, deleteriously affecting the function of the myocardium. On echocardiogram, this is manifest by abnormal wall motion (hypokinesia) of absent wall motion (akinesia).

Because the ventricle is inadequately emptied, ventricular end-diastolic pressure and volumes increase. This is transmitted to the atrium. On the left side of the heart, the increased pressure is transmitted to the pulmonary vasculature, and the resultant hydrostatic pressure favors extravasations of fluid into the lung parenchyma, causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillary beds, favoring extravasations of fluid into the tissues of target organs and extremities, resulting in dependent peripheral edema.

1. Coronary Artery Disease
2. Hypertension
3. Valvular Heart Disease

Diastolic Dysfunction: - Diastolic dysfunction (or diastolic heart failure) occurs when the heart contracts normally, but the ventricles do not relax properly or are stiff, and less blood enters the heart during normal filling. Heart failure caused by diastolic dysfunction is generally described as the backward failure of the ventricle to adequately relax and typically denotes a stiffer ventricular wall. The "stiffness" and contractility of the ventricular walls in diastole was first described by Pierre-Simon Laplace. This caused inadequate filling of the ventricle and therefore results in an inadequate stroke volume (SV). SV is a mathematical term amenable to manipulation of many variables. The failure of ventricular relaxation also results in elevated end-diastolic pressures, and the end result is identical to the case of

systolic dysfunction (pulmonary edema in left heart failure, peripheral edema in right heart failure).

Diastolic dysfunction may not manifest itself except in physiologic extremes if systolic function is preserved. The patient may be completely asymptomatic at rest. However, they are exquisitely sensitive to increases in heart rate, and sudden bouts of tachycardia (which can be caused simply by physiological responses to exertion, fever, or dehydration, or by pathological tachyarrhythmias such as atrial fibrillation with rapid ventricular response) may result in flash pulmonary edema. Adequate rate control (usually with a pharmacological agent that slows down AV conduction such as a calcium channel blocker or a beta-blocker) is, therefore, of key importance to preventing acute decomposition.

Left ventricular diastolic function can be determined through echocardiography by measurement of various parameters such as the E/A ratio (early-to-artial left ventricular filling ratio), the E (early left ventricular filling) deceleration time, and the isovolumic relaxation time.

1. Hypertension
2. Hypertrophic Obstructive cardiomyopathy (HCM)
3. Restrictive Cardiomyopathy

A calculation done during an echocardiogram, called the ejection fraction (EF), is used to measure ho well you heart pumps with each beat to help determine if systolic dysfunction is present. Your doctor can discuss which condition you have.

Clinical Presentation of CHF

The clinical presentation of HF comprises symptoms of shortness of breath (SOB)/dyspnea (sensitivity of 84%-100%, but a specificity of 17%-34%); orthopnea /SOB on lying own (sensitivity of 22%-50% and a specificity of 74%-77%); paroxysmal nocturnal dyspnea (sensitivity 39%-41%, specificity form 80%-84%); fatigue/weakness/lethargy (due to HF-induced circulation-related abnormalities in skeletal muscles); edema, abdominal distention and right hypochondrial pain (most likely due to right-sided heart failure with sensitivity and specificity of 23% and 80%, respectively). Due to compensatory mechanisms, early stages of HF lack specific signs; however, late stages of HF demonstrate the following signs: tachycardia (99% specificity and 7% sensitivity); pedal edema (93% specificity and 10% sensitivity); increased jugular venous pressure (JVP) (usually>6cm; specificity of 92%and sensitivity of 39%), abnormal lung sounds (crackles) (specificity of 78% and sensitivity of

60%); S3 gallop (specificity of 99% and sensitivity of 13%). Other signs, such as hepatojugular reflux and ascites, are not found frequently in HF, but have a specificity of 96% and 97%, while a sensitivity of 24% and 1%, respectively. Recent research has uncovered the micro vascular dysfunction and subsequent decrease in 02 supplies or mismatch with the 02 supply vs. demand in HF patients. Therapeutic strategies to improve muscle micro vascular and oxidative function via exercise training, anti-inflammatory and antioxidant agents have been proposed to be essential to provide better exercise tolerance and quality of life. HF has primarily been recognized as a disease of the elderly population (>60 years) and is reported to affect about 2%-3% of people in the United States. Of these include 10% of males and 8% of females. Unfortunately, these numbers are on a gradual increase due to the on-going prevalence of HF with increasing age. In the USA itself, about more than three million physician visits per year have been accounted for patients with HF as the primary health issue. In 2013, the total number of HF patients were 5.1 million, and direct costs were equal to $32 billion; and this cost is being projected to increase by about three-fold by 2030. As of 2011, the estimated lifetime cost of HF per individual patient was $110,000/year, with more than three fourths of this cost consumed by 'in-hospital care'. Interestingly, the five-year mortality rate for HF was reviewed to be approximately 50%, which is significantly higher than that of some cancers. Among Medicare patients, 30-day all-cause, risk-standardized mortality rates for HF are 10%-12%, while 30-day, all-cause, risk-standardized readmission rates after hospital discharge are 20%-25%. There is indeed a slight decrease in HF-related mortality from 2000 to 2014. The age-adjusted rate for HF-related mortality was 105.4 per 100,000 populations in 2000 and reached 84.0 per 1000,000 in 2014. Similarly, the percentage of in hospital HF-related deaths declined from 42%.6% in 2000 to 30% in 2014. Furthermore, although in a nursing home or long-term care facility, the percentage of deaths have been decreased from 30.1% in 2000 to 26.7% in 2014, such deaths have increased in the patients in residence and in outpatient clinics or hospice care by about 10% and 7%, respectively. Although the prognosis of other cardiac conditions, such as acute coronary syndrome (ACS), severe hypertension, valvular and congenital heart diseases, has improved over the past decade, the prevalence of HF has increased in a relatively exponential manner. An increase in the prevalence of co-morbid conditions and risk factors, such as increased body mass index (BMI), metabolic syndrome, elevated apolipoprotein B/apolipoprotein A ratio and cigarette smoking, in these populations with relatively increased

life expectancy may be some of the reasons behind the increased prevalence of HF. Furthermore, available treatment options for HF only offer symptomatic relief and lack definitive curative treatment for the affected heart. As far as hospitalization is concerned, acute decompensate heart failure (ADHF) is the most common form of heart failure that accounts for~80% of hospitalizations related to heart failure. The common causes of ADHF include non-adherence to medication or dietary restrictions; uncontrolled hypertension; acute coronary syndrome/ischemia; dysrhythmia/arrhythmias and COPD exacerbation; alcohol intoxication or excess; thyroid conditions; pregnancy; and other iatrogenic conditions, such as postoperative fluid replacement or administration of steroids or non-steroidal anti-inflammatory drugs; all directly or indirectly leading to the progression of the underlying disease.

Causes of Congestive Heart Failure: -

1. Coronary artery disease: -Coronary artery disease (CAD), a disease of the arteries that supply blood and oxygen to the heart, causes decreased blood flow to the heart muscle. If the arteries become blocked or severely narrowed, the heart becomes starved for oxygen and nutrients.

2. Heart attack: - A heart attack occurs when a coronary artery becomes suddenly blocked, stopping the flow of blood to the heart muscle. A heart attack damages the heart muscle, resulting in a scarred area that does not function properly.

3. Conditions that overwork the heart: - Conditions including high blood pressure, valve disease, thyroid disease, diabetes, or heart defects present at birth can all cause heart failure can occur when several diseases or conditions are present at once.

Sings: -

    a. Pulmonary rales
    b. Pulmonary edema
    c. S3 gallop
    d. Cool extremities
    e. Pleural effusion
    f. Cheyne-Strokes respiration
    g. Tachycardia
    h. Narrow pulse pressure

    i.   Cardiomegaly

    j.   Peripheral edema

    k.   Jugular venous distension

    l.   Hepatojugular reflux

    m. Hepatomegaly

Symptoms of heart failure: -

You may not have any symptoms of heart failure, or the symptoms may be mild to severe. Symptoms can be constant or can come and go. The symptoms can include:

Congested lungs. Fluid backup in the lungs can cause shortness of breath with exercise or difficulty breathing at rest or when lying flat in bed. Lung congestion can also cause a dray, hacking cough or wheezing. Fluid and water retention. Less blood to your kidneys causes fluid and water retention, resulting in swollen ankles, legs, abdomen (called edema) and weight gain. Symptoms may cause an increased need to urinate during the night. Bloating in your stomach may cause a loss of appetite or nausea. Dizziness, fatigue and weakness less blood to your major organs and muscles makes you feel tired and weak. Less blood tothe brain can cause dizziness or confusion. Rapid or irregular heartbeats the heart beats faster to pump enough blood to the body. This can cause a rapid or irregular heartbeat. If you have heart failure, you may have one or all of these symptoms or you may have none of them. They may or may not indicate a weakened heart.

Diagnosis of Congestive Heart Failure: -

Your doctor will ask you many questions about your symptoms and medical history. You will be asked about any conditions you have that may cause heart failure (such as coronary artery disease, angina, diabetes, heart valve disease, and high blood pressure). You will be asked if you smoke, take drugs, drink alcohol (and how much you drink), and about what drugs you take.

You will also get a complete physical exam. Your doctor will listen to your heart and look for signs of heart failure as well as other illnesses that may have caused your heart muscle to weaken or stiffen.

Your doctor may also order other tests to determine the cause and severity of your heart failure. These include:

1.   Blood tests: - Blood tests are used to evaluate kidney and thyroid function as well as to check cholesterol levels and the presence of anemia. Anemia is a blood condition

that occurs when there is not enough hemoglobin (the substance in red blood cells that enables the blood to transport oxygen through the body) in a person's blood.

2. B-type natriuretic peptide (BNP) blood test: -BNP is a substance secreted from the heart in response to changes in blood pressure that occur when heart failure develops or worsens. BNP blood levels increase when hear failure symptoms worsen, and decrease when the heart failure condition is stable. The BNP level in a person with heart failure – even someone whose condition is stable – may be higher than in a person with normal heart function. BNP levels do not necessarily correlate with the severity of heart failure.

3. Chest X-ray: -A chest X-ray shows the size of your heart and whether there is fluid build-up around the heart and lungs.

4. Echocardiogram: - This test is an ultrasound which shows the heart's movement, structure, and function. Ejection fraction (EF) is used to measure how well your heart pumps with each beat to determine if systolic dysfunction or heart failure with preserved left ventricular function in present. Your doctor can discuss which condition is present in your heart.

5. Electrocardiogram (EKG or ECG): - An EKG records the electrical impulses traveling through the heart. Cardiac catheterization. This invasive procedure helps determine whether coronary artery disease is a cause of congestive heart failure.

6. Stress Test: - non-invasive stress tests provide information about the likelihood of coronary artery disease.

Other tests may be ordered, depending on your condition.

Treatment: -

Heart failure is a chronic disease needing lifelong management. However, with treatment, signs and symptoms of heart failure can improve, and the heart sometimes becomes stronger. Treatment may help you live longer and reduce your chance of dying suddenly.

Doctors sometimes can correct heart failure by treating the underlying cause. For example, repairing a heart valve or controlling a fast heart rhythm may reverse heart failure. But for most people, the treatment of heart failure involves a balance of the right medications and, in some cases, use of devices that help the heartbeat and contract properly.

Surgery and medical devices: -

In some cases, doctors recommend surgery to treat the underlying problem that led to heart failure. Some treatments being studied and used in certain people include:

1. Coronary bypass surgery: - If severely blocked arteries are contributing to your heart failure, your doctor may recommend coronary artery bypass surgery. In this procedure, blood vessels from your leg, arm or chest bypass a blocked artery in your heart to allow blood to flow through your heart more freely.

2. Heart valve repair or replacement: - If a faulty heart valve causes your heart failure, your doctor may recommend repairing or replacing the valve. The surgeon can modify the original valve to eliminate backward blood flow. Surgeons can also repair the valve by reconnecting valve leaflets or by removing excess valve tissue so that the leaflets can close tightly. Sometimes repairing the valve includes tightening or replacing the ring around the valve (annuloplasty). Valve replacement is done when valve repair isn't possible. In valve replacement surgery, the damaged valve is replaced by an artificial (prosthetic) valve. Certain types of heart valve repair or replacement can now be done without open heart surgery, using either minimally invasive surgery or cardiac cauterization techniques.

3. Implantable cardioverter-defibrillators (ICDs): -An ICD is a device similar to a pacemaker. It's implanted under the skin in your chest with wires leading through your veins and into your heart. The ICD monitors the heart rhythm. If the heart starts beating at a dangerous rhythm, or if your heart stops, the ICD tries to pace your heart or shock it back into normal thythm. An ICD can also function as a pacemaker and speed your heart up if it is going too slow. Cardiac resynchronization therapy (CRT), or biventricular pacing. A biventricular pacemaker sends timed electrical impulses to both of the heart's lower chambers (the left and right ventricles so that they pump in a more efficient, coordinated manner. Many people with heart failure have problems with their heart's electrical system that cause their already-weak heart muscle to beat in an uncoordinated fashion. This inefficient muscle contraction may cause heart failure to worsen. Often a biventricular pacemaker is combined with an ICD for people with heart failure.

4. Ventricular assist devices (VADs): - A VAD, also known as a mechanical circulatory support device, is an implantable mechanical pump that helps pump blood from the lower chambers of your heart (the ventricles) to the rest of your body. A VAD is implanted into the abdomen or chest and attached to a weakened heart to help it pump

blood to the rest of your body. Doctors first used heart pumps to help keep heart transplant candidate alive while they waited for a donor heart. VADs may also be used as an alternative to transplantation. Implanted heart pumps can enhance the quality of life of some people with severe heart failure who aren't eligible for or able to undergo heart transplantation or are waiting for a new heart.

5. Heart transplant: - Some people have such severe heart failure that surgery or medications don't help. They may need to have their diseased heart replaced with a healthy donor heart. Heart transplants can improve the survival and quality of life of some people with severe heart failure. However, candidates for transplantation often have to wait long time before a suitable donor heart is found. Some transplant candidates improve during this waiting period through drug treatment or device therapy and can be removed from the transplant waiting list.

A heart transplant isn't the right treatment for everyone. A team of doctors at a transplant center will evaluate you to determine whether the procedure may be safe and beneficial for you.

Drug Used in Congestive Heart Failure: -

Inotropic drugs

a) Cerdiac glycosides

Digoxin, Digitoxin, ouabain

b) Sympathomimetics

Dobutamine, Dopamine

c) Phosphodiesterase III inhibitors

Amrinone, Milrinone

Diuretics

a) High ceiling diuretics:

Frrosemide, Bumetanide

b) Thiazide like diuretics

Hydrochlorothiazide. Metolazone, Xipamide

B-Adrenergic blockers

Metoprolol, Bisoprolol, Carvedilol

Aldosterone antagonist

Spironolactone, Eplerenone

Inhibitors of rennin-Angiotensin Aldosterone System

a) ACE-inhibitors

Enalapril, Ramipril, etc.

b) Angiotensin (AT1 receptor) antagonists Valsartan, Telmesartan, Lostratan and others.

Vasodilators

a) Venodilator

Glyceryl trinitrate and other nitrates

b) Arteriolar dilator

Hydralazine

c) Arteriolar+Venodilator

Sodium Nitroprusside

Vndaqely

Generic Name: taramidis meglumine

Dosage Form: capsule, liquid filled.

Drug Class:-Transthyretin Stabilizer

Company: Pfizer Inc.

Treatment for: Cardiomyopathy of Transthyretin-Mediated Amyloidosis.

1. Indications and usage

Vyndaqel and VYNDAMAX are indicated for the treatment of the cardiomyopaythy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.

2. Dosage and administration

Recommended Dosage

The recommended dosage is either Vyndaqel 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily.

VYNDAMAX and Vyndaqel are not substitutable on a per mag basis

Administration Instructions The capsules should be swallowed whole and not crushed or cut.

If a dose is missed, instruct patients to take the dose as soon as remembered or to skip the missed dose and take the next dose at the regularly scheduled time. Do not double the dose.

3. Dosage forms and strengths

Vyndaqel is available as:

Tafamidis meglumine 20 mg: yellow, ,opaque, oblong capsule, printed with "VYN20" in red.

VYNDAMAX is available as:

Tafamidis 61 mg: reddish brown, opaque, oblong capsule printed with "VYN 61" in white.

4. Contraindications

None

5. Adverse reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The date reflect exposure of 377 ATTR-CM patients to 20 mg or 80 mg (administered as four 20mg capsules) of Vyndaqel administered daily for an average of 24.5 months (ranging from 1 day to 111 months).

Adverse events were assessed from ATTR-CM clinical trails with Vyndaqel, primarily a 30-month placebo-controlled trial [see Clinical Studies (14)]. The frequency of adverse events in patients treated with Vyndaqel 20 mg (n=88) or 80 mg (n=176; administered as four 20-mg capsules) was similar to that with placebo(n=177).

In the 30-month placebo-controlled trail, similar proportions of Vyndaqel-treated patients and placebo-treated patients discontinued the study drug because of an adverse evetn: 12 (7%), 5 (6%), and 11 (6%) from the Vyndaqel 80-mg, Vyndaqel 20-mg, and lplacebo groups, rspectively.

6. Drug interactions

BCRP Substrates

Tafamidis inhibits breast cancer resistant protein (BCRP) in vitro and may increases exposure of substrates of this transporter (e.g., methotrexate. rosuvastatin, imatinib) following Vyndaqel 80 mg or VYNDAMAX 61 mg. Dose adjustment may be needed for these substrates.

7. Use in specific populations

Pregnancy Risk Summary

Based on findings from animal studies, Vyndaqel and VYNDAMAX may cause fetal harm when administered to a pregnant woman. However, limited available human data with Vyndaqel use in pregnant women (at a dose of 20 mg per day) have not identified any drug-

associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of tafamidis meglumine to pregnant rabbits during organogenesis resulted in adverse effects on development (embryofetal mortality, fetal body weight reduction and fetal malformation) at a dosage providing approximately 9 times the human exposure (AUC) at the maximum recommended Human dose (MRHD) of Vyndaqel (80 mg), and increased incidence of fetal skeletal variation at a dosage providing equivalent human exposure (AUC) at the MRHD. Postnatal mortality, growth retardation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation at a dosage approximately 2 times the MRHD based on body surface area (mg/m2) (see Data). Advise pregnant women of the potential risk to a fetus. Report pregnancies to the Pfizer reporting line at 1-800-438-1985.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In pregnant rats, oral administration of tafamidis meglumine (0, 15, 30, and 45 mg/kg/day) throughout organogenesis resulted in decreased fetal body weights at >30 mg/kg/day (approximately 10 times the human exposure at the MRHD based on AUC). The no-observedadverse-effect-level (NOAEL) for embryofetaql development in tats was 15 mg/kg/day (approximately 7 times the human exposure at the MRHD based on AUC.

In pregnant rabbits, oral administration of tafamidis meglumine (0, 0.5, 2, and 8 mg/kg/day) throughout organogenesis resulted in increased embryo fetal mortality, reduced fetal body weights, and an increased incidence of fetal malformations at 8 mg/kg/day (approximately 9 times the human exposure at the MRHD based on AUC), which was also maternally toxic. Increased incidences of fetal skeletal variations were observed at doses >0.5 mg/kg/day (approximately equivalent to the human exposure at the MRHD based on AUC).

In the pre- and postnatal study, pregnant rates received oral administration of tafamidis meglumine at doses of 0, 5, 15, or 30 mg/kg/day throughout pregnancy and lactation (Gestation Day 7 to Lactation Day 20). Decreased survival and body weights, delayed male

sexual maturation and neurobehavioral effects 9learning and memory impairment) were observed in the offspring of dams treated at 15 mg/kg/day (approximately 2 times the MRHD on a mg/m2 basis). The NOAEL for pre- and postnatal development in rats was 5 mg/kg/day (approximately equivalent to the MRHD on a mg/m2 basis).

Risk Summary

There are no available data on the presence of tafamidis in human milk, the effect on the breastfed infant, or the effect on milk production. Tafamidis is present in rat milk (see Data). When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on findings from animal studies which suggest the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatme.

Geriatric Use No dosage adjustment is required for elderly patients (>65 years) [see Clinical Pharmacology (12.3)]. Of the total number of patients in the clinical study (n=441), 90.5% were 65 and over, with a median age of 75 years.

8. Overdosage

There is minimal clinical experience with overdose. During clinical trials, two patients accidentally ingested a single Vyndaqel dose of 160 mg without adverse events. The highest does of tafamidis meglumine given to healthy volunteers in a clinical trail was 480 mg as a single dose. There was 480 mg as a single dose. There was one reported adverse event of mild hordeolum at this dose.

9. Description

Vyndaqel (trafamidis meglumine) and VYNDAMAX (tafamidis contain tafamidis as the active moiety, which is a selective stabilizer of transthyretin.

The chemical more of tafamidis meglumine is 2-(3,5-dichlorophenyly)-1,3-benzoxazole-6carboxylic acid mono (1-deoxy-1-methylamino-D-glucitol). The molecular formula is C14H7CI2NO3 c7H17N05, and the molecular weight is 503.33 g/mol. The structural formula is: Tafamidis meglumine 20-mg soft gelatin capsule for oral use contains a white to pink colored suspension of tafamidis meglumine 20 mg (equivalent to 12.2. mg of tafamidis free acid), and the following inactive ingredients: ammonium hydroxide 28%, brilliant blue FCF, carmine, ethyl alcohol, gelatin, glycerin, iron oxide 9yellow), isopropyl alcohol, polyethylene glycol 400, polysorbate 80, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitan monooleate, sorbitol, and titanium dioxide.

The chemical name of tafamidis is 2-(3,5-dichlorophenyl)-1,3-benzoxazole-6-carboxylic acid. The molecular formula is C14H7CI2NO3, and the molecular weight is 308.12 g/mol.

Tafamidis 61-mg soft gelatin capsule for oral use contains a white to pink colored suspension of tafamidis 61 mg and the following inactive ingredients: ammonium hydroxide 28%, butylated hydroxytoluene, ethyl alcohol, gelatin, glycerin, iron oxide 9red), isopropyl alcohol, polyethylene glycol 400, polysorbate 20, povidone (K-value 90), polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol, and titanium dioxide.

10. Clinical pharmacology

Mechanism of Action Tafamidis is a selective stabilizer of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.

Pharmacodynamics A proprietary TTR stabilization assay was utilized as a pharmacodynamic marker and assessed the stability of the TTR tetramer ex vivo. The TTR stabilization assay quantifies immunoturbidimetric measurement of the stable TTR tetramer in plasma pre-and posttreatment with 2-day in vitro denaturation with urea. Using this proprietary assay, a dosedependent trend for greater TTR tetramer stabilization is observed for Vyndaqel 80-mg compared to Vyndaqel 20-mg. However, the clinical relevance of a outcomes is not known.

Vyndaqel stabilized both the wild type TTR tetramer and the tetramers of 14 TTR variants tested clinically after once-daily dosing. Trfamidis also stabilized the TTR tetramer for 25 variants tested ex vivo.

Vyndaqel land VYNDAMAX may decrease serum concentrations of total thyroxine, without an accompanying change in thyroid stimulating hormone (TSH). This reduction in total thyroxine values is probably the result of reduced thyroxine binding to or displacement from transthyretin (TTR) due to the high binding affinity of tafamidis to the TTR thyroxine receptor. No corresponding clinical findings consistent with hypothyroidism have been observed.

Biomarkers associated with heart failure (NT-proBNP and Troponin I) favored Vyndaqel over placebo.

Cardiac Electrophysiology

At approximately 2.2 times the steady steady state peak plasma concentration (Cmax) at the recommended dose, tafamidis does not prolong the QTc interval to any clinically relevant extent.

Pharmacokinetics

No clinically significant differences in steady state Cmax and area under the plasma concentration over time curve (AUC) of tafamidis were observed for VYNDAMAX61-mg capsule compared to Vyndaqel administered as four 20-mg capsules.

Tafamidis exposure increases proportionally over single (up to 480 mg) or multiple (up to 80 mg) (1 to 6 times the approved recommended dosage) once daily dosing.

The apparent clearance were similar after single and repeated administration of Vyndaqel 80 mg.

Absorption

Median tafamidis peak concentrations occurred within 4 hours following dosing.

Effect of Food

No clinically significant differences in the pharmacokinetics of tafamidis were observed following administration of a high fat, high calorie meal.

Distribution

The apparent steady state volume of distribution of tafamidis is approximately 18.5 liters. Plasma protein binding of tafamidis is >99% in vitro. Tafamidis primarily binds to TTR.

Elimination

The mean half-life of tafamidis is approximately 49 hours. The apparent oral clearance of tafamidis is 0.263 L/hr. The degree of drug accumulation at steady state after repeated tafamidis daily dosing is approximately 2.5-fold greater than observed after a single dose.

Metabolism

The metabolism of tafamidis has not been fully characterized. However, glucuronidation has been observed.

Excretion

After a single oral dose of tafamidis meglumine 20 mg, approximately 59% of the dose was recovered in feces (mostly as the unchanged drug) and approximately 22% of the dose was recovered in urine (mostly as the glucuronide metabolite).

Clinical Results

FDA Approval

The FDA approval was based on a multicentre, international, randomized, double-blind. Placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM. Patients were randomized in a 1:2:2 ration to receive Vyndaqel 20 mg (n=88), Vyndaqel 80 mg (administered as four 20-mg Vyndaqel capsules) (n=176), or matching placebo (n=177) once daily for 30 months, in addition to standard of care (e.g., diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). Transplant patients were excluded from this study. The analysis demonstrated a significant reduction in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled Vyndaqel 20 mg and 80 mg arms versus placebo. Analysis of the individual components of the primary analysis (all-cause mortality and cardiovascular-related hospitalizations) also demonstrated significant reductions for Vyndeaqel versus placebo.

Side Effects: -

Sings of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face lips, tongue, or throat.

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