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Management and Role of Pharmacist in Chronic Heart Failure

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ABSTRACT

Heart Failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. This is further subdivided into HF with reduced left ventricular ejection fraction (HFrEF) or HF with preserved left ventricular ejection fraction (HFpEF) previously known as diastolic HF. HF may be caused by disease of the myocardium, pericardium, endocardium, heart valves, vessels, or by metabolic disorders. Most patients with HFrEF should be routinely treated with guideline directed medical therapy (GDMT) that includes an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. Selected patients should also receive loop diuretics, hydralazine/nitrates, or aldosterone antagonists. The benefits of these medications on slowing HF progression, reducing morbidity and mortality, and/or improving symptoms are clearly established, Digoxin is potentially beneficial in symptomatic patients with HFrEF already receiving optimal medical therapy to decrease HF hospitalizations. There is little clinical trial evidence to guide which treatment are optimal to use in HFrEF.

Keywords: Heart Failure, Angiotensin-converting enzyme.

INTRODUCTION

Heart failure (HF), also known as **chronic heart failure** (**CHF**), is when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs.[1][2][3]

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.[4][5] These cause heart failure by changing either the structure or the functioning of the heart.[4]. The severity of disease is graded by the severity of symptoms with exercise.[6]

Classification of (HF) 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). The two types of 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 is affected, or the heart's ability to relax.[4] 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[7]. HFpEF is further categorized as borderline HF if the EF stays between 41% and 49% and improved HF if EF is more than 40%[8].
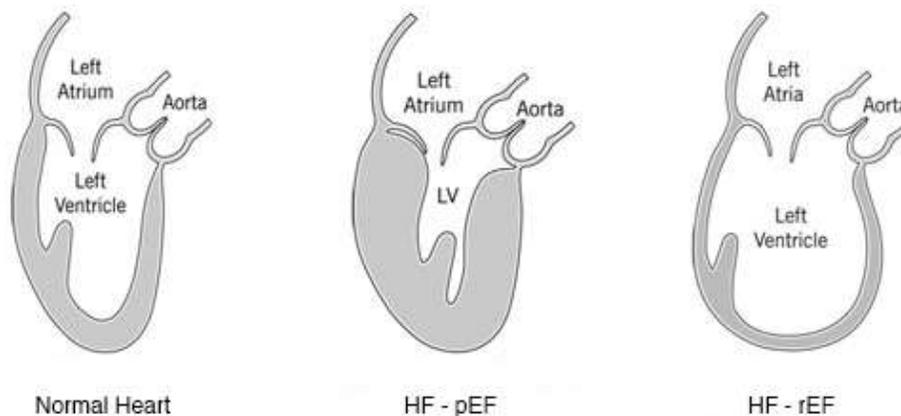
In contrast, in patients with HFrEF, the LV cavity is typically dilated, and the ratio of LV mass/end-diastolic volume is either normal or reduced. At the cellular level, both cardio myocyte diameter and the volume of myofibrils are higher in HFpEF than in HFrEF[8]. As far as treatment and outcome are 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[7][9][10].

The New York Heart Association (NYHA) functional classification defines four functional classes as:

Class I: HF does not cause limitations to physical activity; ordinary physical activity does not cause symptoms.

Class II: HF causes slight limitations to physical activity; the patients are comfortable at rest, but ordinary physical activity results in HF symptoms.

Class III: HF causes marked limitations of physical activity; the patients are comfortable at rest, but less than ordinary activity causes symptoms of HF.

Class IV: HF patients are unable to carry on any physical activity without HF symptoms or have symptoms when at rest.

The American College of Cardiology/American Heart Association (ACC/AHA) staging system is defined by the following four stages:

Stage A: High risk of heart failure, but no structural heart disease or symptoms of heart failure;

Stage B: Structural heart disease, but no symptoms of heart failure;

Stage C: Structural heart disease and symptoms of heart failure;

Stage D: Refractory heart failure requiring specialized interventions[11].

Pathophysiology of Heart failure

The heart of a person with heart failure may have a reduced force of contraction due to overloading of the ventricle. In a healthy heart, increased filling of the ventricle results in increased contraction force (by the Frank–Starling law of the heart) and thus a rise in cardiac output. In heart failure, this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched heart muscle.[12]

A common finding in those with heart failure is an increased heart rate, stimulated by increased sympathetic activity[13] in order to maintain an adequate cardiac output. Initially, this helps compensate for heart failure by maintaining blood pressure and perfusion, but places further strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease. Sympathetic activity may also cause potentially fatal abnormal heart rhythms. An increase in the physical size of the heart's muscular layer may occur. This is caused by the terminally differentiated heart muscle fibers increasing in size in an attempt to improve contractility. This may contribute to the increased stiffness and thus decrease the ability to relax

during diastole. Enlargement of the ventricles can also occur and contributes to the enlargement and spherical shape of the failing heart. The increase in ventricular volume also causes a reduction in stroke volume due to mechanical and inefficient contraction of the heart.[14]

The general effect is one of reduced cardiac output and increased strain on the heart. This increases the risk of cardiac arrest (specifically due to abnormal ventricular heart rhythms) and reduces blood supply to the rest of the body. In chronic disease the reduced cardiac output causes a number of changes in the rest of the body, some of which are physiological compensations, some of which are part of the disease process:

- Arterial blood pressure falls. This destimulates baroreceptors in the carotid sinus and aortic arch which link to the nucleus tractus solitarii. This center in the brain increases sympathetic activity, releasing catecholamines into the blood stream. Binding to alpha-1 receptors results in systemic arterial vasoconstriction. This helps restore blood pressure but also increases the total peripheral resistance, increasing the workload of the heart. Binding to beta-1 receptors in the myocardium increases the heart rate and makes contractions more forceful in an attempt to increase cardiac output. This also, however, increases the amount of work the heart has to perform.

- Increased sympathetic stimulation also causes the posterior pituitary to secrete vasopressin (also known as antidiuretic hormone or ADH), which causes fluid retention at the kidneys. This increases the blood volume and blood pressure.

- Heart failure also limits the kidneys' ability to dispose of sodium and water, which further increases edema.[15] Reduced blood flow to the kidneys stimulates the release of renin – an enzyme which catalyses the production of the potent vasopressor angiotensin. Angiotensin and its metabolites cause further vasoconstriction, and stimulate increased secretion of the steroid aldosterone from the adrenal glands. This promotes salt and fluid retention at the kidneys.

- The chronically high levels of circulating neuroendocrine hormones such as catecholamines, renin, angiotensin, and aldosterone affect the myocardium directly, causing structural remodelling of the heart over the long term. Many of these remodeling effects seem to be mediated by transforming growth factor beta (TGF-beta), which is a common downstream target of the signal transduction cascade initiated by catecholamines[16] and angiotensin II,[17] and also by epidermal growth factor (EGF), which is a target of the signaling pathway activated by aldosterone[18]

- Reduced perfusion of skeletal muscle causes atrophy of the muscle fibers. This can result in weakness, increased fatigue ability and decreased peak strength – all contributing to exercise intolerance.[19]

Management of Heart Failure

Management of heart failure requires a multimodal approach. It involves a combination of lifestyle modifications, medications, and possibly the use of devices or surgery.

Lifestyle Changes

People with CHF are educated to undertake various non-pharmacological measures to improve symptoms and prognosis. Such measures include:[20]

- Moderate physical activity, when symptoms are mild or moderate; or bed rest when symptoms are severe.

- If sleep apnea is identified, treat with CPAP, BiPAP, dental appliances or surgery. Sleep apnea is an under-recognized risk factor for heart failure

- Weight reduction – through physical activity and dietary modification, as obesity is a risk factor for heart failure and left ventricular hypertrophy.

- Monitor weight – this is a parameter that can easily be measured at home. Rapid weight increase is generally due to fluid retention. Weight gain of more than 2 pounds is associated with admission to the hospital for heart failure[21]

- Sodium restriction – excessive sodium intake may precipitate or exacerbate heart failure, thus a "no added salt" diet (60–100 mmol total daily intake) is recommended for patients with CH

1.   Fluid Restriction

According to a review in 2009, there is apparently no evidence of benefit of fluid restriction in patients with clinically stable heart failure otherwise receiving optimal pharmacological treatment.[22] The same review suggested that clinicians still choosing to restrict fluid intake for patients with HF should consider an individualized fluid prescription, potentially based on patient body weight, sodium intake, and likelihood of adherence.[22]

Generally water intake should be limited to 1.5 L daily or less in patients with hyponatremia, though fluid restriction may be beneficial regardless in symptomatic reduction.

2.   Medications

There is a significant evidence–practice gap in the treatment of CHF; particularly the underuse of ACE inhibitors and β-blockers and aldosterone antagonists which have been shown to provide

mortality benefit.[23] Treatment of CHF aims to relieve symptoms, to maintain a euvolemic state (normal fluid level in the circulatory system), and to improve prognosis by delaying progression of heart failure and reducing cardiovascular risk. Drugs used include: diuretic agents, vasodilator agents, positive inotropes, ACE inhibitors, beta blockers, and aldosterone antagonists (e.g., spironolactone). Some drugs which increase heart function, such as the positive inotrope milrinone, lead to increased mortality, and are contraindicated.[24][25]

1.   Angiotensin Modulating agents

Unless contraindicated or not tolerated, ACE inhibitor (ACE) therapy is recommended for all patients with systolic heart failure, irrespective of symptomatic severity or blood pressure.[26][27][28] ACE inhibitors improve symptoms, decrease mortality and reduce ventricular hypertrophy. Angiotensin II receptor antagonist therapy (also referred to as AT_1-antagonists or angiotensin receptor blockers), particularly using candesartan, is an acceptable alternative if the patient is unable to tolerate ACEI therapy.[29][30] ACEIs and ARBs decrease afterload by antagonizing the vasopressor effect of angiotensin, thereby decreasing the amount of work the heart must perform. It is also believed that angiotensin directly affects cardiac remodeling, and blocking its activity can thereby slow the deterioration of cardiac function.

A number of studies have been done to investigate whether ACE i plus ARB is better than an ACEi treatment alone in reducing death, disability or hospital admission in CHF with systolic dysfunction. The two largest studies were CHARM-Added and Val-HeFT.[31][32] The conclusion of a Cochrane Database Systematic Review, which included these two studies and five others, was that combining ACEi treatment with ARB was not effective in reducing total mortality RR 0.98 [95% CI 0.9, 1.06] or cardiovascular mortality RR 0.93 [95% CI 0.84, 1.03] when compared with single therapy of an ACEi. Combined therapy did reduce HF-related hospital admissions with an absolute risk reduction of 4.4% but also increased discontinuation of medication due to adverse effects with an absolute risk increase of 3.7**%.**[33] In plain English, 23 people would need to be treated to reduce one hospitalization for HF while treating 27 people would harm one person with adverse effects. Thus, combined therapy does not improve mortality and may slightly increase morbidity.

2.   Diuretics

Diuretic therapy is indicated for relief of congestive symptoms. Several classes are used, with combinations reserved for severe heart failure:[20]

- Loop diuretics (e.g. furosemide, bumetanide) – most commonly used class in CHF, usually for moderate CHF

- Thiazide diuretics (e.g. hydrochlorothiazide, chlorthalidone, chlorthiazide) – may be useful for mild CHF, but typically used in severe CHF in combination with loop diuretics, resulting in a synergistic effect.

- Potassium-sparing diuretics (e.g. amiloride) – used first-line use to correct hypokalaemia.

- Spironolactone is used as add-on therapy to ACEI plus loop diuretic in severe CHF.

- Eplerenone is specifically indicated for post-MI reduction of cardiovascular risk.

If a heart failure patient exhibits a resistance to or poor response to diuretic therapy, ultrafiltration or aquapheresis may be needed to achieve adequate control of fluid retention and congestion. The use of such mechanical methods of fluid removal can produce meaningful clinical benefits in patients with diuretic-resistant heart failure and may restore responsiveness to conventional doses of diuretics.[28]

Newly emerging evidence showed that glucocorticoids could be used in the treatment of decompensated heart failure to potentiate renal responsiveness to diuretics, especially in heart failure patients with refractory diuretic resistance with large dose of loop diuretics.[33] [34] [35] [36] [37] [38] [39] Glucocorticoids induce a potent diuresis in heart failure because they could improve renal responsiveness to atrial natriuretic peptide by up regulating natriuretic peptide receptor A NPR-A expression in the renal inner medullary collecting duct, inducing a potent diuresis.[40]

3.   Beta Blockers

Until recently (within the last 20 years), β-blockers were contraindicated in CHF, owing to their negative inotropic effect and ability to produce bradycardia – effects which worsen heart failure. However, current guidelines recommend β-blocker therapy for patients with systolic heart failure due to left ventricular systolic dysfunction after stabilization with diuretic and ACEI therapy, irrespective of symptomatic severity or blood pressure.[28] As with ACEI therapy, the addition of a β-blocker can decrease mortality and improve left ventricular function. Several β-blockers are specifically indicated for CHF including: bisoprolol, carvedilol, nebivolol and extended-release metoprolol. The antagonism of β_1 inotropic and chronotropic effects decreases the amount of work the heart must perform. It is also thought that catecholamines and other sympathomimetics have an effect on cardiac remodeling, and blocking their activity can slow the deterioration of cardiac function.

4.   Positive Inotropes

Digoxin (a mildly positive inotrope and negative chronotrope), once used as first-line therapy, is now reserved for control of ventricular rhythm in patients with atrial fibrillation; or where adequate control is not achieved with an ACEI, a beta blocker and a loop diuretic.[28] There is no evidence

that digoxin reduces mortality in CHF, although some studies suggest a decreased rate in hospital admissions.[41] It is contraindicated in cardiac tamponade and restrictive cardiomyopathy.

The inotropic agent dobutamine is advised only in the short-term use of acutely decompensated heart failure, and has no other uses.[28]

Phosphodiesterase inhibitors such as milrinone are sometimes utilized in severe cardiomyopathy. The mechanism of action is through inhibiting the breakdown and thereby increasing the concentration of cAMP similar to beta adrenoreceptor agonism, resulting in inotropic effects and modest diuretic effects.

5.   Alternative Vasodilators

The combination of isosorbide dinitrate/hydralazine is the only vasodilator regimen, other than ACE inhibitors or angiotensin II receptor antagonists, with proven survival benefits. This combination appears to be particularly beneficial in CHF patients with an African American background, who respond less effectively to ACEI therapy[42][43]

6.   Aldosterone receptor antagonists

The RALES trial[44] showed that the addition of spironolactone can improve mortality, particularly in severe cardiomyopathy (ejection fraction less than 25%.) The related drug eplerenone was shown in the EPHESUS trial [45] to have a similar effect, and it is specifically labelled for use in decompensated heart failure complicating acute myocardial infarction. While the antagonism of aldosterone will decrease the effects of sodium and water retention, it is thought that the main mechanism of action is by antagonizing the deleterious effects of aldosterone on cardiac remodeling.

7.   Recombinant neuroendocrine hormones

Nesiritide, a recombinant form of B-natriuretic peptide, is indicated for use in patients with acute decompensated heart failure who have dyspnea at rest. Nesiritide promotes diuresis and natriuresis, thereby ameliorating volume overload. It is thought that, while BNP is elevated in heart failure, the peptide that is produced is actually dysfunctional or non-functional and thereby ineffective

8.   Vasopressin receptor antagonists

Tolvaptan and conivaptan antagonize the effects of antidiuretic hormone (vasopressin), thereby promoting the specific excretion of free water, directly ameliorating the volume overloaded state, and counteracting the hyponatremia that occurs due to the release of neuroendocrine hormones in an attempt to counteract the effects of heart failure. The EVEREST trial, which utilized tolvaptan, showed that when used in combination with conventional therapy, many symptoms of acute decompensated heart failure were significantly improved compared to conventional therapy

alone[46] although they found no difference in mortality and morbidity when compared to conventional therapy.[47]

Devices

CRT: People with NYHA class III or IV, left ventricular ejection fraction (LVEF) of 35% or less and a QRS interval of 120 ms or more may benefit from cardiac resynchronization therapy (CRT; pacing both the left and right ventricles), through implantation of a bi-ventricular pacemaker. This treatment modality may alleviate symptoms, improving quality of life, and in some trials has been proven to reduce mortality.

The COMPANION trial demonstrated that CRT improved survival in individuals with NYHA class III or IV heart failure with a widened QRS complex on an electrocardiogram.[48] The CARE-HF trial showed that patients receiving CRT and optimal medical therapy benefited from a 36% reduction in all-cause mortality and a reduction in cardiovascular-related hospitalization.[49]

However, around one third of patients with LVEF of 35% of less have a QRS complex duration of 120 ms or more. In the remaining two thirds of patients (who have a QRS complex duration of 120 ms or less), CRT may actually be harmful.[50][51]

CCM: Cardiac Contractility Modulation (CCM) is a treatment for patients with moderate to severe left ventricular systolic heart failure (NYHA class II–IV) which enhances both the strength of ventricular contraction and the heart's pumping capacity. The CCM mechanism is based on stimulation of the cardiac muscle by non-excitatory electrical signals (NES), which are delivered by a pacemaker-like device. CCM is particularly suitable for the treatment of heart failure patients with normal QRS complex duration (120 ms or less) and has been demonstrated to improve the symptoms, quality of life and exercise tolerance of heart failure patients.[52][53][54][55][56]] CCM is approved for use in Europe, but not currently in North America.[57][58]

AICD: Patients with NYHA class II, III or IV, and LVEF of 35% (without a QRS requirement) may also benefit from an implantable cardioverter-defibrillator (ICD), a device that is proven to reduce all-cause mortality by 23% compared to placebo in patients who were already optimally managed on drug therapy.[59][60] Patients with severe cardiomyopathy are at high risk for sudden cardiac death due to ventricular dysrhythmias. Although ICDs deliver electrical shocks to resynchronize heart rhythm which are potentially distressing to the patient, they have not been shown to affect quality of life.[61] The number of (appropriate and inappropriate) shocks seems to be associated with a worse outcome.[62] Although they are expensive, ICDs are potentially cost-effective in this setting.[63]

LVAD: Another current treatment involves the use of left ventricular assist devices (LVADs). LVADs are battery-operated mechanical pump-type devices that are surgically implanted in the

upper part of the abdomen. They take blood from the left ventricle and pump it through the aorta. LVADs are becoming more common and are often used in patients waiting for heart transplants.

Role of Pharmacist in the management of Heart failure

Numerous studies have shown that community-based pharmacists, as part of multidisciplinary TOC teams, can improve outcomes for patients with HF[64][65][66] Educate the patient to understand the need for treatment and the benefits and risks offered by prescribed medication before concordance with a treatment plan can be reached, appropriate patient education is necessary to encourage an understanding of their condition and how prescribed drug treatment will work and affect their daily lives. Admission medication reconciliation and discharge medication review were performed to monitor for appropriateness and dosing, duplications, omissions, and drug interactions. Since its initiation, the program has increased compliance with HF core measures (including appropriate medication use) and reduced HF readmissions, 30-day readmissions, all-cause readmissions, and costs[66]

Patients should be made aware that diuretics will increase urine production, and that doses are usually timed for the morning to avoid nocturea. Counsel the patient to monitor and record their weight on daily basis, to detect fluid retention and modify Diuretic dosages. Timing of doses is also important, if a nitrate regimen is being used, then patients must be made aware that the last dose of the nitrate should be taken mid to late afternoon to ensure that a nitrate free period occur overnight, reducing the risk of nitrate tolerance. Where renal function is compromised, careful attention to dosage selection is required for drug excreted largely unchanged in the urine.

Medications contraindicated in patients with heart failure.

(Adapted from Amabile 2004 and Page 2016—Source: American Heart Association, Inc) [67][68][69][70]

Medication/medication class	Recommendation	Primary reasons for contraindication/caution
Corticosteroids	Conservative use; lowest doses	Sodium and fluid retention
Nonsteroidal anti-inflammatory drugs	Avoid in patients with symptomatic left ventricular dysfunction	Sodium and water retention Compromise effects of diuretics Increase systemic vascular resistance
Antiarrhythmic agents (class I and III, excluding amiodarone)	Avoid all class I agents Avoid ibutilide and sotalol	Negative inotropic activity Proarrhythmic effects
Antihypertensive agents		
α1-antagonists	Do not use	Cardiac hypertrophy

Non-dihydropyridine calcium channel blockers	Avoid use	Negative inotropic activity Neurohormonal activation
Minoxidil	Avoid use	Fluid retention Stimulation of RAAS
Antihyperglycemic agents		
Metformin	Avoid use in patients with NYHA class III/IV symptoms and those with previous hospitalization for HF exacerbations; conservative use with monitoring in others	Increased anaerobic glucose metabolism and lactate elevation
Alogliptin and saxagliptin	Avoid use in patients who develop signs and symptoms of HF, especially if the patient has CV or renal disease at baseline	Unknown
Thiazolidinediones	Avoid use in patients with NYHA class III/IV symptoms; monitor for new or increased HF symptoms in others	Fluid retention
Hematologic medications		
Anagrelide	Avoid	Positive inotropic activity Tachycardia
Cilostazol	Do not use	Inhibition of phosphodiesterase III
Neurologic and psychiatric medications		
Amphetamines	Avoid use	Peripheral α- and β-agonist activities Tachycardia, arrhythmia
Carbamazepine	Avoid if possible; use other first-line agents	Negative inotropic and chronotropic effects Suppression of sinus nodal automaticity and atrioventricular conduction Anticholinergic effects
Clozapine	Actively monitor for new or increased HF symptoms	Unknown
Ergot alkaloids	Avoid use if possible; if used, monitor regularly for new murmurs	Increased serum norepinephrine Excess serotonin activity
Pergolide	Avoid use if possible	Excess serotonin levels
Tricyclic antidepressants	Avoid if possible; use other first-line agents	Negative inotropic effects Increase in automaticity Slowing of intracardiac conduction Proarrhythmic
Miscellaneous medications		
β_2-agonists	Avoid long-term systemic administration	Direct positive chronotropic effect Hypokalemia

Herbal medications	Avoid	Unknown; lack of data for most Increased risk of bleeding Hypertension Sodium retention
Itraconazole	Avoid	Negative inotropic activity
Sulfamethoxazole/trimethoprim	Avoid in patients taking an ACEi or ARB	Risk of hyperkalemia and sudden death
Theophylline	Avoid use in decompensated HF	Increased theophylline levels and toxicity
TNF-α inhibitors	Avoid if new-onset or worsening HF symptoms develop; infliximab doses of > 5 mg/kg contraindicated	Cytokine-mediated myocardial toxicity

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *CV* cardiovascular, *HF* heart failure, *NYHA* New York Heart Association, *RAAS* renin–angiotensin–aldosterone system, *TNF-α* tumor necrosis factor alpha Number of issues around the safe use of medication must be considered. There is an increased risk of drug-drug and drug-disease interactions, it is important to aware of clinically important interactions and to investigate potentially problematic combinations, as well as to regularly assess the patient for any signs or symptoms of drug therapy problems, monitoring for problems such as negative inotropic effects, excessive blood pressure reduction, salt and fluid retention should be undertaken and, where appropriate laboratory measurement of serum drug concentration (Digoxin) or physiological markers (Potassium, creatinine) should be performed to confirm or exclude adverse effect**.**

CONCLUSION

Heart failure is one of the most common and costly diseases, and the number of HF-related deaths is increasing. Pharmacists are integral to multidisciplinary TOC teams in HF. During the transition from hospital to ambulatory home- or community-based care, pharmacy services (including medication reconciliation, identification and prevention of adverse drug events, suggestions for improving medication access, and patient education) can improve outcomes and decrease the risk for hospitalization. Cohesive multidisciplinary team approaches can improve medication adherence and provide a trusted resource for patients' questions. Novel technologies and expanded access to pharmacy services can improve current limitations of transitional care in HF and other chronic diseases.

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