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THERAPY IN PRACTICE

Managing Therapeutic Competition in Patients with Heart Failure, Lower Urinary Tract Symptoms and Incontinence

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Abstract Up to 50 % of heart failure patients suffer from lower urinary tract symptoms. Urinary incontinence has been associated with worse functional status in patients with heart failure, occurring three times more frequently in patients with New York Heart Association Class III and IV symptoms compared with those with milder disease. The association between heart failure and urinary symptoms may be directly attributable to worsening heart failure pathophysiology; however, medications used to treat heart failure may also indirectly provoke or exacerbate urinary symptoms. This type of drug–disease interaction, in which the treatment for heart failure precipitates incontinence, and removal of medications to relieve incontinence worsens heart failure, can be termed therapeutic competition. The mechanisms by which heart failure medication such as diuretics, angiotensin-converting enzyme (ACE) inhibitors and β-blockers aggravate lower urinary tract symptoms are discussed. Initiation of a prescribing cascade, whereby antimuscarinic agents or β3-agonists are added to treat symptoms of urinary urgency and incontinence, is best avoided. Recommendations and practical tips are provided that outline more judicious management of heart failure patients with lower urinary tract symptoms. Compelling strategies to improve urinary outcomes include titrating diuretics, switching ACE inhibitors, treating lower urinary tract infections, appropriate fluid management, daily weighing, and uptake of pelvic floor muscle exercises.

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1 Introduction

While medications are essential for palliating symptoms and improving survival, prescription of additional medications for one condition may commonly precipitate or worsen other co-morbidities. Therapeutic competition is a type of bidirectional drug–disease interaction that occurs when treatment for the first condition adversely impacts the second, and subsequent treatment of the second condition exacerbates the first [1]. An important example of therapeutic competition is between heart failure treatment and urinary incontinence, a common geriatric syndrome. Urinary incontinence reduces dignity, autonomy and mood in later life and should be prevented at all costs [2]. This article reviews the mechanisms and possible solutions for managing therapeutic competition between heart failure and lower urinary tract symptoms in older adults.

Heart failure affects 1–3 % of the general population [3, 4]. The prevalence of lower urinary tract symptoms is much higher, reported to occur in over 50 % of men and women [5]. Urinary frequency, urinary urgency, nocturia and urinary incontinence are among the most common lower urinary tract symptoms [5, 6]. Urinary incontinence can be subclassified into stress, urgency, and mixed or functional incontinence. Involuntary urine leakage that occurs with coughing, laughing or sneezing is called stress incontinence and is caused by intravesicular pressures that exceed urethral closing pressures. Urgency incontinence is associated with a sudden, compelling urge to void, and often coexists with other symptoms of overactive bladder such as frequency, urgency and nocturia. Functional incontinence has typically been described in frail older adults with mobility or cognitive impairment, and refers to the inability to reach the toilet in time to void [7].

Studies indicate that 35–50 % of heart failure patients suffer from urinary incontinence [8–10]. Urinary incontinence is associated with reduced functional capacity in older adults with heart failure [11]. Although urinary symptoms may antedate the diagnosis of heart failure, urinary urgency with or without incontinence is found to be 2.9 times (95 % CI 1.3–6.3) more prevalent in patients with New York Heart Association Class III or Class IV heart failure compared with Class I or Class II. This suggests that worsening heart failure either provokes or exacerbates urinary symptoms [12]. A direct association between heart failure pathophysiology and bladder dysfunction may explain this relationship; or perhaps other co-morbidities such as diabetes mellitus or renal failure play a role [13–15]. Alternatively, medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors and β-blockers, which are frequently prescribed for patients with heart failure, may indirectly be at cause.

Mr. S. is an 84-year-old man recently admitted to hospital with decompensated heart failure. He had an ST-elevation myocardial infarction 10 years ago and again last year. Prior to his admission he was active and well. Upon discharge his medications included Monopril® 10 mg orally daily, furosemide 40 mg orally twice daily, aldactone 25 mg orally twice daily, bisoprolol 5 mg orally daily, atorvastatin 20 mg orally daily, metformin 850 mg orally twice daily, acetylsalicylic acid (ASA, aspirin) 80 mg orally daily, pantoprazole 40 mg orally daily, and oxazepam 15 mg orally every night. Three months post-discharge he has become increasingly depressed, and is no longer enjoying activities such as golfing with his friends. He experiences urinary urgency eight to ten times per day, four times nightly, and regularly leaks urine on the way to the toilet. He is reluctant to go out for fear of leakage and odor. His self-esteem is low, he does not want to wear protective undergarments and he is rapidly losing the will to live.

2 Mechanisms Underlying the Risk of Lower Urinary Tract Symptoms in Heart Failure Patients

Direct precipitation of lower urinary tract symptoms during heart failure can be due to compensatory secretion of natriuretic peptides [16]. Natriuretic peptides play an important role in the body's regulation of intravascular volume by promoting excretion of sodium and elimination of bodily fluid. A number of natriuretic peptides have been identified: atrial natriuretic peptide, urodilantin, brain natriuretic peptide (BNP), C-type natriuretic peptide and Dendroaspis natriuretic peptide [16]. BNP has been widely studied in relation to cardiac load, with levels typically rising and falling in association with the severity of heart failure symptoms. Released from ventricular cardiomyocytes in response to an increase in ventricular wall tension, BNP has been shown to fluctuate in parallel with hemodynamic measures such as left ventricular end diastolic pressure. Binding of BNP to the natriuretic peptide A receptor stimulates a signaling cascade that results in natriuresis and inhibition of renin and aldosterone. Both European and North American heart failure guidelines recognize value in measuring BNP levels as a diagnostic and prognostic biomarker of heart failure in patients with dyspnea [17, 18]. High BNP levels have been independently associated with the presence and severity of nocturnal voiding, as well as nocturnal polyuria in elderly patients [19]. Redistribution and elimination of fluid from peripheral or pulmonary edema further contribute to urinary frequency and excessive diuresis, especially at night when peripheral edema is resorbed in the supine position.

Chronic heart failure patients experience fatigue and may also become deconditioned due to dyspnea-related activity restriction. In patients with New York Heart Association class III–IV symptoms, reduced functional capacity and decreased mobility are important risk factors for urinary incontinence, as both impede the ability to reach the toilet in a timely manner during episodes of urinary urgency [11]. Predisposing risk factors for lower urinary tract symptoms, such as pelvic floor muscle weakness, obesity, or consumption of caffeinated beverages, may synergistically augment the risk of incontinence in the presence of heart failure pathology. Exacerbation of pre-existing symptoms of incontinence can also occur.

Indirect effects of both acute and chronic heart failure on the lower urinary tract may be mediated by prescription of medications for both tertiary prevention and symptomatic relief. Drug therapy in heart failure is essential for slowing disease progression and for improvement of symptoms and survival [20]. However, as a part of their modes of action or as side effects, many of these medications can iatrogenically contribute to urinary frequency, urgency, nocturia or incontinence [8, 21–23].

3 Heart Failure Medications that Precipitate or Worsen Urinary Incontinence

Although diuretics are typically used to relieve congestion, and ACE inhibitors and angiotensin receptor blockers (ARBs) improve survival, these classes of drugs have been suggested to accelerate and worsen urinary symptoms in the presence of heart failure. β-blockers are also frequently prescribed for heart failure patients and can potentially

have an impact on the lower urinary tract. Because heart failure, urinary problems and use of these medications are common in old age, this is above all a geriatric complication.

3.1 Diuretics

Diuretics are part of the first-line treatment for symptomatic relief of heart failure. These drugs increase sodium urinary excretion and decrease physical signs of fluid retention [24]. Clinical trials have shown that the use of diuretics leads to a reduction in venous pressure, edema and body weight [25], with the consequence of providing symptomatic relief and improvement of quality of life for patients with heart failure and preserved systolic function [26]. These symptomatic benefits occur more rapidly with diuretics than for other heart failure drugs. The long-term effects include improvement in cardiac function and exercise tolerance, with positive effects on morbidity and mortality [24].

Nonetheless, the desired actions of diuretics in heart failure—increased urine sodium excretion and volume of urine—can also cause urinary frequency, urgency and incontinence [27]. There are, however, differences between loop diuretics and non-loop diuretics, where loop diuretics have been more often associated with urinary tract symptoms. Use of loop diuretics has been related to increased urinary frequency and urgency [28], whereas non-loop diuretics have not.

Studies on incontinence are conflicting. Cross-sectional analyses have suggested that diuretics may be implicated in causing incontinence [29, 30], whereas longitudinal studies have not confirmed this finding [31, 32].

The later stages of heart failure are characterized by fluid overload and a chronic state of overhydration. At this stage, even high doses of loop diuretics might prove ineffective, a phenomenon known as diuretic resistance [33, 34]. An important mechanism behind diuretic resistance is functional adaptation of the distal tubule after chronic exposure to loop diuretics. One way to overcome the problem is to add diuretics acting on different sites of the nephron [34]. Typically, a thiazide-type diuretic, hydralazine, or other potassium-sparing or mineralocorticoid diuretics are combined with loop diuretic therapy to attain diuretic synergy. This is common clinical practice, although there is a lack of high-level evidence for use of this combination. While the combination therapy can prove effective for resistant patients, it can also cause hypokalemia and worsening renal function [33]. Additionally, the synergistic effects of combination therapy may cause heavy diuresis, potentially aggravating urinary frequency and urgency in late-stage heart failure patients. However, this has, to our knowledge, not yet been investigated.

3.2 Angiotensin-Converting Enzyme (ACE) Inhibitors

ACE inhibitors are standard therapy in heart failure patients with symptomatic left ventricular systolic dysfunction. They have been shown to reduce morbidity and mortality in clinical trials; however, there is less evidence for treatment with ACE inhibitors in all patients with heart failure and in those with preserved ejection fraction [35]. Although ACE inhibitors are generally well tolerated, they are associated with a persistent cough probably caused by increased levels of bradykinin and tachykinin. The ACE inhibitor-induced cough is characterized by being dry, nonproductive and worse at night [36], and occurs in 5–35 % of patients taking ACE inhibitors [37]. This cough can produce or exacerbate stress incontinence by increasing urethral pressure. A number of case reports have described cough-induced stress incontinence upon initiation of an ACE inhibitor, which remits upon discontinuation [38, 39]. One case series reported a 10 % incidence of severe drug-induced stress incontinence in diabetic post-menopausal women initiating ACE inhibitors [40].

3.3 β-Blockers

β-Blockers have been extensively studied in the treatment of heart failure, and are standard treatment for improvement of clinical outcomes of heart failure patients [41]. There is a chronic activation of the sympathetic nervous system in heart failure in an attempt to restore cardiac output. This is a compensatory mechanism that provides inotropic support to the failing heart by increasing stroke volume and peripheral vasoconstriction. However, these measures eventually accelerate disease progression and negatively affect survival [42]. β-Blockers affect heart failure by inhibiting sympathetic nervous system activation. This effect has been shown to reduce morbidity and mortality in several clinical trials [20]. In the context of incontinence, emerging evidence suggests that β-blockers may increase bladder contractility and provoke symptoms of urinary urgency [30, 43]. The effects of β-blockers on the risk of incontinence are, however, inconsistent [44, 45] and require further investigation.

4 Overactive Bladder Medications that Precipitate or Worsen Heart Failure

Avoidance of prescribing cascades in the elderly is a key tenet of pharmacologic management in this population. Increased urinary frequency and urgency due to diuretic dose escalation during acute heart failure episodes may motivate patients to consult for incident symptoms of overactive bladder. The overactive bladder syndrome

comprises symptoms of urinary urgency, with or without urinary frequency and nocturia, in the presence or absence of urgency urinary incontinence [6]. Consultation for overactive bladder may lead to prescription of one of two oral pharmaceutical classes of medication for the treatment of overactive bladder symptoms. Both antimuscarinic agents and β3-adrenergic agonists have proven efficacy for reducing symptoms of urinary frequency, urgency and incontinence [46, 47]. If a proper medication history is not ascertained, and neither the patient nor the consultant makes the link between heart failure medications and urinary symptoms, a prescribing cascade for the treatment of overactive bladder may ensue.

4.1 Antimuscarinic Agents

Antimuscarinic drugs are the mainstay of treatment for patients with symptoms of overactive bladder, including urgency incontinence. Blockade of M2 and M3 receptors in the bladder detrusor muscle reduces urinary urgency, frequency and urgency incontinence. However, blockade of muscarinic cholinergic receptors (primarily M2 subtype) on sinoatrial nodal cells can also potentially increase heart rate, which is best avoided in patients with heart failure [48]. Several antimuscarinic agents are approved for the treatment of overactive bladder syndrome, all with different relative affinities for the M2 subtype [48]. QT interval prolongation and induction of polymorphic ventricular tachycardia (torsade de pointes) are other theoretical concerns with the use of antimuscarinic agents in heart failure patients [48]; however, few studies have specifically investigated whether antimuscarinic agents exert these effects in the real-life setting. Based on available information, any effects that exist appear to be modest and their clinical relevance unknown. Data suggest that the prevalence of cardiovascular co-morbidities is significantly higher in patients with than without overactive bladder, and that cardiovascular co-morbidities are found to be more prevalent in treated versus untreated patients (58.8 vs. 53.7 %; $p < 0.001$). The association between antimuscarinic agents and cardiovascular adverse events therefore warrants further investigation [49, 50].

4.2 β3-Adrenoceptor Agonists

The β3-adrenoceptor subtype is dominant in the human detrusor muscle, and activation of the β3-adrenoceptor mediates relaxation of the detrusor during the storage phase of the micturition cycle, improving bladder storage capacity without impeding bladder voiding [47]. Mirabegron is a selective β3-adrenoceptor agonist approved for the treatment of overactive bladder. β3-adrenoceptors are thought to account for more than 95 % of all β-adrenergic messenger RNA in the human bladder, and are highly and preferentially expressed on urinary bladder tissues, including the urothelium, interstitial cells and detrusor smooth muscle [47]. Concern about cross-reactivity with β1- and β2-adrenoceptor subtypes found in the vasculature and cardiac muscle, as well as direct stimulation of β3-adrenoceptors in the heart, have raised concern about the cardiac safety of mirabegron in heart failure patients [51].

A meta-analysis of three randomized clinical trials with a pool of over 2,760 patients looked at treatment-emergent adverse effects due to mirabegron [47]. Adverse effects included hypertension (odds ratio [OR] 0.91, 95 % CI 0.68–1.21) and cardiac arrhythmias (OR 1.67, 95 % CI 0.95–2.92, $p = 0.07$). These results suggest no obvious effect of β3-agonists on cardiac function in participants in these trials. However, interpretation must be made with caution as the study population was not representative of elderly patients with multiple morbidities and chronic heart failure, although many were on β-blockers for the treatment of hypertension. Further research is warranted on the specific effects of β3-agonists in heart failure patients, as well as the combined use of β-blockers and β-agonists in this population.

> At Mr. S's 3-month follow-up visit his depression is apparent. He is disheveled and talks about constantly needing to run to the toilet. Screening questions reveal that he experiences urge incontinence which is affecting his sense of dignity. Dyspnea on exertion and orthopnea are absent. Pedal edema is minimal. His skin turgor is low and he complains of dry mouth. Urinalysis is negative. His diabetes is well-controlled but his renal function has worsened. He has started drinking two bottles of beer in the evening. Mr. S. does not know why he is taking oxazepam; he says it was prescribed upon discharge from hospital. He wants to know if there are medications to take to control his urine leakage.

5 Management of Therapeutic Competition in Patients with Heart Failure and Urinary Symptoms

Recommendations and practical tips for the management of heart failure patients with lower urinary tract symptoms entail a variety of pharmacological modifications and non-pharmacological interventions. Figure 1 illustrates different therapeutic approaches to patients with stress incontinence, symptoms of urinary frequency and urgency—including urgency incontinence—and nocturia. A sudden change in urinary symptoms may signal newly decompensated heart failure or the presence of a urinary tract infection. These possibilities should be ruled out and

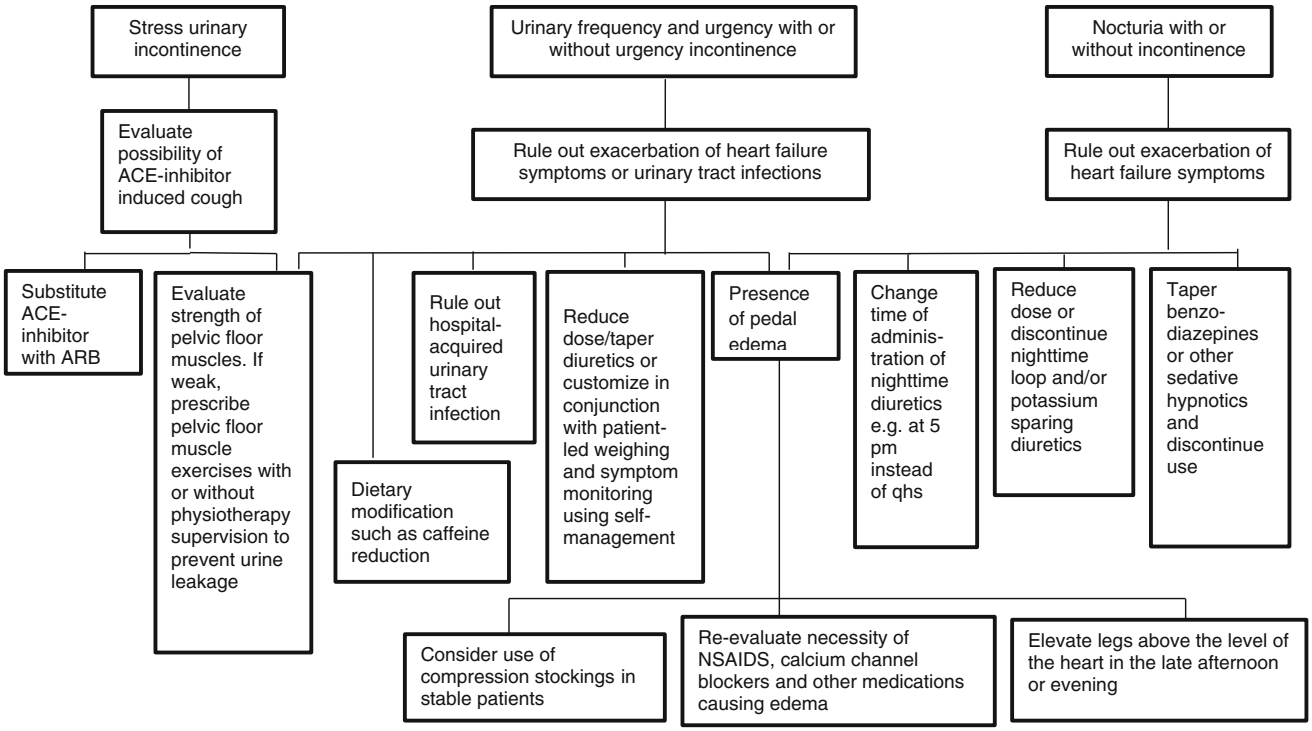

Fig. 1 Management algorithm in patients with chronic heart failure and urinary symptoms. *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *qhs* every night, *NSAIDs* non-steroidal anti-inflammatory drugs

addressed prior to proceeding with other management strategies.

5.1 Dose Reduction of Diuretics

Consider reassessing the need and reducing the dose of diuretics if the patient is otherwise stable. Although complete discontinuation of diuretics can lead to decompensation and relapse [52], many patients are discharged from hospital after an acute episode with high-dose oral diuretics, equivalent to the intravenous doses that were required to relieve symptoms upon admission. When acute congestion is cleared, the lowest dose should be used that is compatible with stable signs and symptoms.

5.2 Substitution of ACE Inhibitors with Angiotensin Receptor Blockers

ARBs do not inhibit degradation of bradykinin, thought to be responsible for the ACE inhibitor-induced cough. ARBs and ACE inhibitors are equal in terms of reduction of mortality and morbidity in heart failure patients, but discontinuation due to adverse effects is lower with ARBs [53]. Therefore, switching to an ARB may be an alternative to avoid the side effect of coughing and consequent stress incontinence associated with ACE inhibitor use [40, 53].

5.3 Rule-Out Reversible Causes of Hospital-Related Morbidity

(a) *Catheter-induced urinary tract infection* Patients in cardiogenic shock or those admitted with acute heart failure who have difficulty voiding often have a urinary catheter inserted to monitor urinary output. In-dwelling catheters provide a nidus for bacterial entry into the normally sterile lower urinary tract, and increase the risk of lower urinary tract infection. Exacerbation of lower urinary tract symptoms including urinary frequency, urgency, nocturia and incontinence post-hospitalization for acute heart failure may indicate the presence of a new urinary tract infection. Attribution of symptoms to an increased dose of diuretics may confound early diagnosis and treatment, especially as dysuria and hematuria are less commonly seen as presenting symptoms and signs of urinary tract infection in the elderly [54]. Recent guidance from the American Board of Internal Medicine for adult hospital medicine recommends that urinary catheters not be placed, or left in place, to monitor urinary output in non-critically ill patients, and that weights should be used instead to track diuresis [55].

(b) *Sedative-hypnotic prescriptions* Admission to the intensive care or coronary care unit for treatment of acute heart failure elicits anxiety among patients as they

grapple with the impending possibility of mortality. Anxiety, combined with the need to reduce adrenergic stimulation and sleeplessness due to the beeps and disruptions inherent to any high-intensity monitoring unit, often leads to prescription of a sedative hypnotic [56]. Evidence suggests that many of these sedative-hypnotic prescriptions persist upon discharge, with hospitalization conferring a 2.7-fold greater risk of incident use than outpatient visits [57]. Medications that bind to $GABA_A$ receptors in the central nervous system can potentially affect the lower urinary tract system either directly, by causing relaxation of striated pelvic floor muscles and/or by interfering with afferent sensory messages from the bladder, or even indirectly through an effect on mobility and toileting ability [21, 58]. For this reason, as well as many others, sedative-hypnotic medications are not recommended in elderly heart failure patients and should be tapered and discontinued. Cognitive behavioral therapy is a safer and equally efficacious alternative to treat insomnia in the ambulatory care setting [59].

5.4 Fluid Management

Fluid restriction represents a key management strategy in patients with chronic heart failure. An individualized fluid management program is recommended for each patient according to the severity of heart failure, renal function and other dietary behaviors. Clinically, 1.5–2 litres per day is recommended for most patients and an intake greater than 2 litres per day is generally discouraged. Patient education with or without provision of self-management strategies for fluid management, sodium restriction, daily weighing and physical conditioning may attenuate urinary problems in heart failure patients, although formal trials are required to test the efficacy of this approach [60, 61]. Patients with recurrent fluid retention who are able to follow instructions can be taught to adjust their diuretic dose based on symptoms of dyspnea on exertion and orthopnea and changes in daily body weight. Use of compression stockings during the day by stable chronic heart failure patients may help prevent distal leg edema, nocturnal fluid redistribution, and nocturnal urinary frequency and urgency [62]. The benefit of compression stockings in patients with decompensated heart failure remains unclear, as the use of compression stockings has been reported to increase right atrial and pulmonary pressures [63].

5.5 Dietary Modification

Caffeinated beverages, such as tea, coffee and colas, may increase urinary urgency and enhance diuresis via the stimulatory effect of caffeine on the bladder detrusor muscle [64, 65]. Even though randomized trials of caffeine reduction in heart failure patients are lacking, epidemiologic data suggest that caffeine intake equivalent to 2 cups (234 mg) or greater than 3 cups (392 mg) of coffee per day is significantly associated with having moderate to severe urinary incontinence in men (1.72, 95 % 1.18–2.49; and 2.08, 95 % 1.15–3.77, respectively), even when adjusting for underlying prostate conditions [66]. Studies of women also reveal that there may be a physiologic link between high caffeine intake, diuresis, and prevalent and incident urgency incontinence [67, 68]. Moderate sodium restriction may also be effective in reducing hospital readmission rates for chronic heart failure patients [69]. Alcohol consumption has been shown to increase the risk of mortality in chronic heart failure patients, although the physiologic mechanism is unclear [70]. Attention to dietary factors should therefore be recommended as part of any conservative management strategy.

5.6 Pelvic Floor Muscle Exercises

Systematic reviews on the effect of pelvic floor muscle training on stress urinary incontinence/mixed urinary incontinence have found that intensive, supervised training can produce clinically important effects on the reduction of urine leakage [71]. Pelvic floor muscle exercises, as part of any conservative management strategy for urgency incontinence, yield equivalent or superior efficacy to pharmacological management, with an uncommon risk of adverse events [72]. Supervision by a trained physiotherapist may augment the effectiveness of pelvic floor muscle training if a patient has difficulty identifying their pelvic floor muscles and/or performing the exercises correctly [73].

5.7 Prescription of Medication for Lower Urinary Tract Symptoms

Although prescription of medication is effective for treating lower urinary tract symptoms, adherence to antimuscarinic agents is poor because of adverse effects such as dry mouth and constipation [74, 75], and the use of β3-agonists has not yet been well-studied in heart failure patients, many of whom are already taking β-blockers. Dry mouth resulting from the use of antimuscarinic agents can paradoxically lead to increased fluid consumption and worsening of heart failure symptoms. Removal of heart failure medications contributing to lower urinary tract symptoms is the preferred management approach, rather than initiating a prescribing cascade and unavoidable therapeutic competition. Conservative management strategies for the treatment of urinary symptoms, such as avoidance of caffeinated beverages and regular

performance of pelvic floor muscle exercises should be prioritized as first-line treatment.

Upon hearing that his diuretics and sleeping pill may be contributing to his urinary symptoms, Mr. S. elects a trial of dose reduction and conservative management. He slowly tapers off the benzodiazepine, experiencing withdrawal symptoms that he controls with sleep hygiene techniques and persistence. A routine of daily weighing, fluid restriction and monitoring of dyspnea symptoms allows him to completely taper off aldactone. He cuts out his morning coffee and bedtime alcohol. He wears compression stockings and every morning practices pelvic floor muscle exercises. Under close surveillance from the cardiac team, he is able to reduce his dose of furosemide to only 20 mg daily. He only wakes up twice nightly to urinate and is able to make it to the toilet on time. Three months later he no longer leaks, is no longer depressed and has resumed playing golf with his friends.

6 Conclusion

Up to 50 % of heart failure patients suffer from lower urinary tract symptoms. Urinary frequency, urgency and incontinence are extremely bothersome, while nocturnal symptoms may disrupt sleep and quality of life. Healthcare practitioners should be aware that medications used to treat heart failure may indirectly provoke or exacerbate urinary symptoms, and that tapering diuretics and switching ACE inhibitors for ARBs are reasonable management approaches. Therapeutic competition may occur as the dose of diuretic is reduced, or new medication is added to treat urinary symptoms. Judicious use of medication, combined with patient collaboration for heart failure and lower urinary symptom self-management are likely the best therapeutic approaches for improving outcomes for these challenging co-morbid conditions.

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