



## Review Article

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# Overactive Bladder is a Distress Symptom in Heart Failure

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The prevalence of Heart failure (HF) is expected to increase worldwide with the aging population trend. The numerous symptoms of and repeated hospitalizations for HF negatively affect the patient's quality of life and increase the patient's economic burden. Up to 50% of patients with HF suffer from urinary incontinence (UI) and an overactive bladder (OAB). However, there are limited data about the relationship between UI, OAB, and HF. The association between HF and urinary symptoms may be directly attributable to worsening HF pathophysiology. A comprehensive literature review was conducted for all publications between January 2000 and November 2017 using the PubMed, Embase, and Cochrane databases. HF represents a major and growing public health problem, with an increased risk of UI and an OAB as comorbidities. Possible effects of HF on urinary problems may be mediated by the prescription of medications for symptomatic relief. Although diuretics are typically used to relieve congestion, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improve survival, these classes of drugs have been suggested to worsen urinary symptoms in the presence of HF. Further research is required to understand the impact of UI and an OAB on the HF illness trajectory.

**Keywords:** Heart failure; Urinary incontinence; Overactive urinary bladder; Prevalence; Comorbidity

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## INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by the reduced ability of the heart to pump and/or fill with blood [1]. HF has been defined as a global pandemic, since it affects around 26 million people worldwide [2]. The prevalence of HF is expected to rise because of the aging population, improvements in the treatment of diagnosed HF, and marked increases in the prevalence of predisposing risk factors such as hypertension and diabetes [1]. In South Korea, the number of patients with HF has been increasing in recent years, with an average annual increase rate of 4.5% from 2009 to 2013 [3]. In addition, HF is one of the

leading causes of death in South Korea [4]. With a rapidly aging population in South Korea, it is expected that the prevalence of HF and its associated costs will continue to increase. HF is characterized by recurrent episodes of exacerbation often preceded by gradually deteriorating fluid status. When it is not adequately assessed and managed, symptoms of volume overload and congestion may eventually develop, which frequently necessitate hospitalization for acute decompensated HF [5].

Urinary incontinence (UI) is defined by the International Continence Society as any involuntary leakage of urine [6]. The overactive bladder (OAB), characterized by urinary urgency, frequency, nocturia, and/or urge incontinence, is common in

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older adults and may be negatively associated with quality of life [7]. Since UI and OAB is an age-related condition, significantly more patients present with concomitant cardiovascular (CV) comorbidities (e.g., hypertension) compared with non-OAB patients [8], which emphasizes the importance of evaluating the CV safety of OAB pharmacotherapies. Also, these comorbid conditions share multiple risk factors such as obesity, diabetes, hypertension, smoking, and advanced age [9]. Particularly, the association between HF and urinary symptoms may be directly attributable to deteriorating HF pathophysiology; however, medications used to treat HF may also indirectly provoke or exacerbate urinary symptoms. For more than half a century, diuretics have been the only drugs that rapidly and efficiently modulate hypervolemia, and these are widely used in patients with HF to correct and maintain optimal fluid status. Because fluid retention and peripheral edema in patients with HF usually necessitate the administration of diuretics, these patients are also likely to experience changes in urinary frequency [10]. However, whether risk factors and medication including diuretics are associated with symptoms of UI and OAB, and worsening quality of life due to HF has not been well-studied [6,11]. Therefore, we conducted this review to compile the existing data on this topic and identify the scope for further studies in this field.

## LITERATURE SEARCH

In this review paper, the articles were identified through the main databases related to health, including the PubMed, Embase, and Cochrane databases to identify English-language peer-reviewed studies published between January 2000 and November 2017. To avoid excluding potential articles, a comprehensive search using both key words and similar terms was conducted. Search terms included “urinary incontinence,” “overactive bladder,” “urinary symptoms or bladder,” “nocturia,” and “heart failure.”

## PREVALENCE AND SIGNIFICANCE OF URINARY INCONTINENCE AND OVERACTIVE BLADDER IN HEART FAILURE

UI is associated with reduced functional capacity in patients with HF [12]. Studies indicate that 35%–50% of patients with HF suffer from UI [13–15]. Although urinary symptoms may antedate the diagnosis of HF, urinary urgency with or without incontinence is found to be 2.9 times more prevalent in patients with New York Heart Association (NYHA) class III or class IV

HF compared with class I or class II [10]. One study reported that 32% of men and 41% of women with chronic HF experience UI [16]. In another study reporting the cooccurrence of chronic diseases and geriatric syndromes in the 2004 wave of the Health and Retirement Study, UI was reported by 36.7% of respondents who also reported having HF [15].

The natural history of OAB in HF patients is not understood. A recent study reported that 34.1% of HF patients experience moderate/severe OAB symptoms, and 43.5% experience moderate/severe lower urinary tract symptoms compared with the age-matched controls [17]. Another study also revealed that the occurrence of OAB symptoms was 57% in patients with chronic HF, although the rate of nonurgent incontinence and urinary frequency and nocturia was 10% and 19%, respectively [10]. However, few patients seek medical treatment for their OAB [10]. It should be noted that patients with chronic HF with OAB may exhibit more severe cardiovascular comorbidities, including hypertension, pulmonary heart disease, cerebrovascular disease, renal disease, and diabetes [18].

Urgency incontinence is associated with a sudden, compelling urge to void, and often coexists with other symptoms of OAB such as frequency, urgency, and nocturia [19]. Unfortunately, many of the bladder control problems experienced by patients with HF may not be cured [20]. Despite this, assessment and treatment by continence or HF healthcare professionals may help reduce patients’ problems to a more manageable level and improve the quality of life and survival rates in HF.

## MECHANISMS AND RISK FACTORS OF URINARY INCONTINENCE AND OVERACTIVE BLADDER IN HEART FAILURE

Direct precipitation of urinary problems in HF may be due to compensatory secretion of natriuretic peptides [20]. Natriuretic peptides play an important role in the body’s regulation of intravascular volume by promoting excretion of sodium and elimination of bodily fluids. Brain natriuretic peptide (BNP) has been widely studied in relation to cardiac load, with levels typically rising and falling in association with the severity of HF 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. High BNP levels have been independently associated with the presence and severity of nocturnal voiding, as well as nocturnal polyuria in elderly

patients [21]. Redistribution and elimination of fluid from peripheral or pulmonary edema further contribute to urinary frequency and excessive diuresis, especially overnight when peripheral edema is resorbed in the supine position [12].

NYHA classification in HF is used to grade the severity of functional limitations of patients and estimate how far they are able to walk before becoming breathless [22]. NYHA class I represents no symptoms, class II represents symptoms during ordinary activities, class III represents symptoms with minimal exertion, and class IV represents symptoms at rest. In patients with NYHA III–IV symptoms, reduced functional capacity and decreased mobility are important risk factors for UI, as both impede the ability to reach the toilet in a timely manner during episodes of urinary urgency [10].

OAB may be a component of a neurohormonal phenomenon that includes HF, fatigue, and depression [10]. Emerging evidence in the fields of neurocardiology and behavioral cardiology exists to suggest that HF and depression share signs such as decreased heart rate variability and symptoms including low mood and fatigue, and researchers suggest they may also share the same mechanism [23,24]. An association between depression and urge incontinence has been reported with depression in 60% of those who have idiopathic urge incontinence [25]. However, the mechanism underlying this relationship is not clear. Choi et al. [26] found decreased heart rate variability in women in OAB, leading them to suggest that OAB symptoms may be indicators of disease or dysfunction in the autonomic nervous system. These findings indicate that further research is needed to better understand the relationship among HF, depression, and OAB.

With regard to risk factors of UI and OAB in HF, effects of both acute and chronic HF on the lower urinary tract may be mediated by the prescription of medications for both tertiary prevention and symptomatic relief [27]. Drug therapy in HF is essential for slowing disease progression and for the improvement of symptoms and survival [11]. 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 [17]. Additionally, many of the risk factors for UI are the same as those for HF, such as advanced age, obesity, obstructive sleep apnea, and diabetes [10,12]. Particularly, patients with chronic HF could harbor several coexisting illnesses, such as hypertension, diabetes, pulmonary disease, and stroke [10]. These comorbidities are also reportedly associated, at least in part, with urologic symptoms in the general population [28–30]. However, there have been few studies on

the frequency and severity of incontinence in patients with HF.

## HEART FAILURE MEDICATIONS THAT WORSEN URINARY INCONTINENCE AND OVERACTIVE BLADDER

Diuretics are part of the first-line treatment for symptomatic relief of HF [31]. These drugs increase sodium urinary excretion and decrease physical signs of fluid retention [31]. Nonetheless, by causing diuresis or increased formation of urine by the kidneys, diuretics increase urinary frequency and may cause urinary urgency and incontinence [32]. While discontinuation of diuretics may lead to “decompensation and relapse” in patients with HF, it is reasonable to reduce the dose after acute congestion has been cleared and the patient is stable [12]. However, whether diuretic use is associated with symptoms of OAB and worsening quality of life has not been well-studied [28]. The role of diuretics in the development of OAB in patients with HF is still a matter of debate because fluid overproduction related to diuretic use may not cause urgency, which is the cardinal symptom of OAB. However, Ekundayo et al. [33] showed that loop diuretics may increase the prevalence of OAB in aged adults. Diuretic-induced rapid production of urine may add urgency to diuretic-associated high urinary frequency.

Angiotensin-converting enzyme (ACE) inhibitors are standard therapy for patients with HF with symptomatic left ventricular systolic dysfunction [12]. 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 HF [34]. Although ACE inhibitors are generally well-tolerated, they are associated with a persistent cough probably caused by increased levels of bradykinin and tachykinin [12]. The ACE inhibitor-induced cough is characterized by being dry, non-productive, and worse at night [35], and occurs in 5%–35% of patients receiving ACE inhibitors [36]. This cough can produce or exacerbate stress incontinence by increasing urethral pressure [12]. Angiotensin receptor blockers (ARBs) for ACE inhibitors are “equal, in terms of reduction of mortality and morbidity in HF patients,” but ARBs do not induce the cough that can cause UI in patients treated with ACE inhibitors [12].

Beta-blockers have been extensively studied in the treatment of HF, and are standard treatment for improvement of clinical outcomes in patients with HF [37]. There is a chronic activation of the sympathetic nervous system in HF 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. In the context of incontinence, emerging evidence suggests that  $\beta$ -blockers may increase bladder contractility and provoke symptoms of urinary urgency [38,39]. The effects of  $\beta$ -blockers on the risk of incontinence are, however, inconsistent and require further investigation.

## NONPHARMACOLOGICAL MANAGEMENT OF URINARY INCONTINENCE AND OVERACTIVE BLADDER IN HEART FAILURE

Lifestyle change is the first step in the management of urinary problems in HF [14]. Namely, conservative management strategies for the treatment of urinary symptoms, such as fluid management, avoidance of caffeinated beverages, and regular performance of pelvic floor muscle exercises should be prioritized as first-line treatment [12,27].

Fluid restriction represents a key management strategy in patients with chronic HF [21,27]. An individualized fluid management program is recommended for each patient according to the severity of HF, renal function, and other dietary behaviors. Clinically, 1.5–2 L of fluid intake per day is recommended for most patients and an intake greater than 2 L per day is generally discouraged [14]. Dietary modifications include the reduction or elimination of caffeinated beverages, which increase urinary urgency and enhance diuresis [27]. Excessive sodium and alcohol consumption should be avoided, as both have a deleterious impact on HF [40]. Use of compression stockings during the day by stable chronic HF patients may help prevent distal leg edema, nocturnal fluid redistribution, and nocturnal urinary frequency and urgency [41,42]. Intensive, pelvic floor muscle exercises, under the supervision of a physical therapist, have been shown to have “clinically important effects” in reducing urine leakage and yield equivalent or superior efficacy to pharmacotherapy with fewer negative effects [27].

## PHARMACOLOGICAL MANAGEMENT OF URINARY INCONTINENCE AND OVERACTIVE BLADDER IN HEART FAILURE

Antimuscarinics represent the most commonly prescribed drugs of OAB and are generally considered to be ‘safe’ drugs [43]. But there are most common adverse cardiac effects related to the use of antimuscarinics such as increase in heart rate and QT interval prolongation [44].

According to a recent review [44], it is difficult to recommend a standardized clinical surveillance of HF patients when treated with antimuscarinics for OAB symptoms. Therefore, clinical and electrocardiography monitoring may be considered in older patients with HF.

To date, mirabegron, a  $\beta_3$ -adrenoceptor agonist, and the first in its class for the treatment of OAB symptoms, offers an efficacious and safe alternative to first-line treatment in patients intolerant to antimuscarinics [45,46]. With regard to the cardiovascular safety of mirabegron, it seems to be good and comparable with that of antimuscarinic agent [45]. However, there are limited data on the use of mirabegron for treating OAB symptoms in HF. Accordingly, further studies are needed to understand the impact of antimuscarinics and mirabegron in patients with HF.

## CONCLUSIONS

UI and OAB are prevalent in patients with HF. Advanced or end-stage HF, fatigue, depression, increased heart rate, and diuretic use are associated with the development of UI and OAB in HF. Moreover, several types of HF medications affect the bladder and its ability to function properly. UI and OAB incontinence can affect health-related quality of life and health status in patients with HF. Additionally, patients with HF may become depressed and be afraid to socialize and enjoy usual activities due to urinary problems. It can also cause prolonged sedentary behaviors or weight gain, which increase the burden on the heart.

Accordingly, urology and HF health professionals should be aware that it is important to assess or monitor urinary problems after HF diagnosis and evaluate the severity of UI and OAB during the HF illness trajectory.

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