



Chronic Pain in Chronic Heart Failure: A Review Article

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Abstract

Heart failure (HF) is one of the main causes of death and disability in the world. The prevalence of HF in developed countries is between 1% and 2% of the adult population and approximately between 6% and 10% in the elderly, giving rise to high costs of care and treatment. Indeed, in the United States, the direct and indirect costs exceeded 23 billion dollars in 2002. HF is typically characterized by periods of acute symptoms followed by returns to nearly asymptomatic periods. As dyspnea and fatigue are considered the signature symptoms of HF, other symptoms such as pain go unnoticed. Awareness of the burden of pain, however, is growing in patients with chronic HF. The past 2 decades have witnessed remarkable technical headway in cardiology and many patients have survived despite the progressive impairment of their cardiovascular function. It is, therefore, of great value to investigate the prevalence and management of pain in patients with HF. To that end, we undertook a comprehensive search using the MEDLINE database for studies and guidelines on the subject of pain and HF and the complications and considerations and finally selected 65 studies for review.

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Introduction

Chronic diseases are now considered the leading cause of morbidity and mortality worldwide. The progression of chronic end-stage organ failure, especially heart failure (HF), is typically marked by a gradual decline punctuated by acute deteriorations in health status and daily functioning.¹ The deterioration of organ failure can be life-threatening and increase the risk of hospital admission and need for intensive treatment.¹⁻³ HF is one of the principal causes of death in the world; the prevalence of this chronic disease in developed countries is from 1% to 2% of the adult population and approximately between 6% and 10% in the elderly. About 15 million people the world over and more than 4.9 million

people in the United States suffer from HF, and the direct and indirect costs of the health care and treatment of these patients are very high.^{1,3} HF is progressive in nature; accordingly, treatment is mainly focused on slowing the progression of the disease and palliating the symptoms of the patients.^{4,5}

Dyspnea and fatigue are deemed the hallmark symptoms of HF, and other symptoms such as pain are liable to go unnoticed.^{6,7} Nonetheless, awareness of the burden of pain and symptoms is growing in patients with HF.^{8,9} Pain in patients suffering from HF may be of different origins by different mechanisms such as ischemia, inflammation, and neuropathy. The experience of pain may diminish cognitive functioning and increase anxiety, sleeplessness, depression, and hopelessness.¹⁰⁻¹² Thus, it is highly beneficial

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to investigate the prevalence of pain and its source and management in patients with HF.

Methods

We undertook a comprehensive search using the MEDLINE database for studies and guidelines on the subject of pain and HF and the complications and considerations thereof. Our search comprised the MeSH headings of heart failure, cardiac failure, congestive heart failure, and heart decompensation, as well as pain and chest pain. We also sought additional articles by performing the same search strategy in the databases of EMBASE, ScienceDirect, and Google Scholar. Subsequently, we combined all the searches and removed the duplicates. The total number of potential articles in our primary search was 245 studies. We thereafter excluded irrelevant articles by reading their title and abstract and finally chose 65 studies for this review article.

Chronic Pain Syndrome in Chronic Diseases

Pain is one of the most common symptoms among individuals seeking medical attention and is identified as the chief complaint on presentation to the emergency department.¹³⁻¹⁵ Patients tend to seek health care for pain not only for diagnostic evaluation and symptom relief but also for the interference of pain with personal performance and the resultant anxiety and emotional distress. When pain persists for weeks or months, the influence of the broader effects of pain on well-being becomes more palpable. Chronic pain can exert negative effects on psychological health and performance of social responsibilities in work and family life.¹⁶ The major challenge in chronic pain is its unusual nature. In this syndrome, the etiology of pain is difficult to identify and the symptoms of pain do not usually respond to the common medical managements. Regardless of its etiology, the chronic pain syndrome affects many aspects of the patient's personal and medical life. The presence of the chronic pain syndrome in the setting of a chronic disease renders patients anxious, frustrated, and depressed-which may have deleterious effects on their therapies.¹⁶

Importance of Pain in Patients with Heart Failure

Patients with HF commonly experience pain in any part of their body. The pain is an important and frequent symptom, particularly during the time of exacerbation and hospitalization.¹⁷ Much as pain has been recognized as the most common identifiable reason for clinical deterioration

prior to admission to the hospital, the importance of pain in patients with HF is frequently underestimated by physicians.¹⁸ It has been shown that patients with HF suffering from pain are older, enjoy lower levels of general health, have more comorbidities, and are even more likely to have a history of cancer than those without HF.¹⁹ The experience of pain may weaken cognitive functioning and increase anxiety, sleeplessness, depression, and hopelessness.¹⁰⁻¹² Furthermore, the presence of pain, particularly when accompanied by fatigue and depression (common findings in HF), may lead to compromised functional performance.²⁰ Moreover, individuals experiencing depression and anxiety tend to have a lower rate of medication adherence, which is an essential component of self-management in patients with HF.²¹ Pain may constitute an important symptom in patients with HF referring to the emergency department. It has been shown that the incidence rate of the acute coronary syndrome among patients with HF presenting to the emergency department with chest pain is 32%. These patients have more prolonged hospital stays, require higher levels of care, and have a higher incidence of death. Given the considerable importance of pain and its management in the setting of HF, we aimed to determine the prevalence of pain and evaluate its management and its impact on the quality of life of patients with HF.

Prevalence of Pain in Patients with Heart Failure

The prevalence of pain in HF varies between 23% and 85% in different studies (Table 1). Although shortness of breath and fatigue are regarded as the most common symptoms of HF, there is a great deal of evidence indicating that pain is a significant symptom in patients with HF (Table 1).²²⁻³³ A remarkable number of studies show that the majority of patients with HF, particularly those with advanced HF, suffer from pain.^{22,23} Interestingly, patients with a lower left ventricular ejection fraction (LVEF) may have significantly higher pain scores than those with a higher LVEF.^{24,25}

Pathophysiology and Source of Pain in Heart Failure

Although the etiology of pain is clear in some instances such as trauma or surgery, the issue of pain in HF is controversial. Pain in chronic illnesses is multifactorial with physiological, sensory, sociocultural, affective, cognitive, and behavioral components. Nevertheless, in patients with HF, the causes of pain or altered pain perception have not been fully explained. Moreover, pain perception may vary from patient to patient and may be altered by other symptoms allied to HF such as shortness of breath, fatigue, depression, and anxiety.³⁴



Table 1. Prevalence of pain in patients with heart failure in different studies

Study	Patient and Study Design	Pain Prevalence	Outcome of Pain	Findings Associated with Increase in Pain
Blinderman et al., 2008 ⁴	Outpatients with end-stage CHF Longitudinal observational study (n=103)	29% (chest pain or pressure) 37% (other types of pain)	High symptom-associated distress being seen in 26.7% of the patients with chest pain and in 54.1% of those with other types of pain	----
Lip et al., 1997 ¹⁴	Hospitalized patients (acute HF) (n=348)	23.1% (chest pain)	----	----
Whelan et al., 2004 ⁷	In hospitalized patients and in a period of 30 days after discharge Prospective cohort study Number of all the patients: 5605 Number of the patients with HF: 428	59% of the total patients (no specific reporting for patients with HF)	----	<ul style="list-style-type: none"> ● Diagnosis-related group weight ● Age > 65 years ● Female gender ● Education level above high school
Nordgren and Sørensen, 2003 ¹⁵	In hospitalized patients (patients with end-stage HF) and in a period of the last 6 months of life Descriptive retrospective design (n=80)	75%	----	----
Godfrey et al., 2007 ¹⁷	Patients with HF at hospital discharge and at 2 and 6 weeks post discharge Part of a larger randomized controlled trial (n=169)	At hospital discharge (68%; n: 115) 68% (n: 78/115) at 2 weeks Post discharge 72% (n: 83/115) at 6 weeks post discharge	Decrease in health-related QOL	<ul style="list-style-type: none"> ● Depression ● Worry ● Feeling a loss of control over one's life ● Feeling as if one was a burden to the family
Goebel et al., 2009 ¹⁹	Veterans with HF Secondary data analysis of a cohort study (n=96)	55.2% (37.5% reporting moderate-to-severe pain)	----	<ul style="list-style-type: none"> ● Increase in overall symptoms
Conley et al., 2015 ²⁰	Outpatients with stable HF Secondary data analysis of a cross-sectional study (n=173)	57%	Pain, fatigue, and depression being associated with decreased functional performance	----
Goodlin et al., 2012 ²²	Outpatients with advanced HF Descriptive multisite study (n=347)	84.4% (39.5% reporting pain at more than 1 site)	----	<ul style="list-style-type: none"> ● Degenerative joint disease ● Other arthritis ● Shortness of breath ● Angina pectoris
Rustøen et al., 2008 ²³	Hospitalized patients with HF Part of a larger descriptive study (n=93)	85% (42.5% reporting severe or very severe pain)	80% of the patients with HF reporting that pain interfered with their normal work In conjunction with the severity of disease and exacerbated mental health, pain having a negative impact on QOL	Higher number of chronic conditions

Table 1. Continued

Shah et al., 2013 ²⁴	Hospitalized patients (acute decompensation of HF) Cross-sectional study (n=100)	60%	----	Lower LVEF ($\leq 40\%$)
Udeoji et al., 2012 ²⁵	Outpatients with stable HF Cross-sectional study (n=62)	52%	----	<ul style="list-style-type: none"> ● Lower LVEF ($\leq 40\%$)
Gan et al., 2012 ²⁶	Chronic HF at a mean follow-up of 22 months Cohort study (not defined in the paper) (n=305)	25.6%	An increase in MACE (patients with moderate-to-severe pain having higher MACE) Decrease in QOL	<ul style="list-style-type: none"> ● Increase in NYHA functional class ● Female gender ● More comorbidities ● Lower LVEF ● Shorter distance during the 6-minute walking test ● Increase in MLHFQ scores ● Increase in TNF-α levels
Pantilat et al., 2016	Patients with HF (classes II and III) Survey at baseline and at 3–6 months' follow-up (n=111)	43% 57% (class III) 32% (class II)	----	Depression (even in mild stage)
Evangelista et al., 2009 ²⁸	Chronic HF Cross-sectional, correlational study (n=300)	67%	Decrease in physical and overall QOL	Worsening functional class
Bekelman et al., 2007 ²⁹	Outpatients with HF Cross-sectional study (n=60)	52% (42% reporting severe pain)	Number of the symptoms being strongly inversely associated with health status as measured by the KCCQ overall score	----
Levenson et al., 2000 ³⁰	Patients with HF during the last 6 months of life A retrospective analysis of data from a prospective cohort study (n=539)	41% of the patients' carers reporting that their patient was in severe pain during the last 3 days before death	Increase in the rate of severe pain in the last 6 months of life	Approach of death
Desbiens et al., 1997 ³¹	Seriously ill hospitalized patients Cross-sectional study Number of all the patients: 1556 Number of the patients with HF: 420	51.2% of all the patients (not defined as HF)	----	<ul style="list-style-type: none"> ● Dyspnea ● Nausea
Desbiens et al., 1997 ³²	Survivors of serious illnesses at 2 and 6 months after discharge Observational cohort study Number of all the patients: 5652 Number of the patients with HF: 104	63% of the patients having reported pain in the hospital also reporting pain at 6 months post discharge	Level of hospital pain being most strongly associated with later pain	During the post-discharge period: <ul style="list-style-type: none"> ● Level of pain during hospitalization ● Increasing age from 18 to 50 years ● Depression ● Increased dependencies in ADLs ● Comorbidity disorders ● Poor QOL ● Anxiety



Table 1. Continued

Desbiens et al., 1996 ³³	Seriously ill hospitalized patients Prospective cohort study Number of all the patients: 5176 Number of the patients with HF: 854	49.9% of the total study population 43.3% of the patients with HF	Dissatisfaction with pain control being more likely reported by the patients with: <ul style="list-style-type: none"> ● More severe pain ● Greater anxiety ● Depression ● Alteration in mental status ● Lower reported income 	<ul style="list-style-type: none"> ● More dependency in ADLs ● More comorbid conditions (especially colon cancer) ● Increasing anxiety ● Depression ● Poor QOL
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CHF, Congestive heart failure; HF, Heart failure; QOL, Quality of life; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiac events; NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire; TNF, Tumor necrosis factor; KCCQ, Kansas City Cardiomyopathy Questionnaire; ADLs, Activities of daily living

Approximately 80% of patients with HF are elderly.³⁵ Multiple sources of pain such as physical, psychological, and neurological have been described in the elderly and they may be the sources of pain in HF. Increase in age has been defined as a marker of increase in pain levels among patients with HF in previous studies.^{15,32} Moreover, comorbid conditions such as cancers and other chronic illnesses increase by age. As a result, the presence of these conditions and the age-related increase in pain are frequently found in patients suffering from HF. The comorbidities presenting with HF that may be the source of pain in these patients include coronary artery disease, chronic obstructive pulmonary disease, cancers, depression, anxiety disorder, peripheral vascular disease, pneumonia, diabetes mellitus, osteoarthritis, and low back pain.³⁰

About one-third of patients with HF suffer from depression and the same proportion of them suffer from anxiety. A meta-analysis showed that major depression after HF was a predictor for subsequent all-cause mortality. Also, depressive mood in the wake of HF is a predictor of cardiovascular mortality.³⁶ There is a strong association between increasing depression and anxiety and greater levels of pain. Also, there is a correlation between dissatisfaction with pain control and level of pain, depression, and anxiety.³³ When death approaches, a significant trend toward an increase in anxiety and depression, as well as increasing rates of severe pain and dyspnea, is observed.³⁰ Table 2 presents the factors contributing to pain in patients with HF.

Cytokines and inflammatory markers may participate in the generation of pain or influence the central processing of pain stimuli.^{37,38} Gan et al.²⁶ evaluated the effects of serum levels of creatinine, NT-proBNP, high-sensitivity C-reactive protein, tumor necrosis factor-alpha (TNF- α), interleukin (IL)-6, and IL-10 on the symptoms of pain in patients with HF and found that only TNF- α levels were higher in those with pain. In the myocardium, the increased expression of TNF- α is associated with reversible and irreversible ischemia/reperfusion injury, post-myocardial infarction remodeling, fetal gene expression, myocyte hypertrophy or apoptosis, and altered endothelial and vascular smooth

muscle cell function-contributing to the development and progression of HF.³⁹

Table 2. Factors associated with pain and increased level of pain in patients with heart failure

1	Physical problems and disabilities
2	Depression, anxiety, and affective disorders
3	(Ischemia) impaired circulation and oxygenation
4	Increase in age
5	Worsening NYHA functional class
6	Increased dependencies in ADLs
7	Female gender
8	Neurohormonal derangement
9	Sensation and neurological conduction
10	Cognition and central nervous system processing
11	Behavior and health literacy
12	Social support and relationships
13	Religious, spiritual, and cultural beliefs
14	Increase in comorbid disorders
15	Poor QOL
16	Approach of death

NYHA, New York Heart Association; ADLs, Activities of daily living; QOL, Quality of life

End-of-life HF is a painful condition influenced by various factors. The theory of "total pain" was defined by Dr. Cicely Saunders in 1984 to conceptualize pain at the end of life.⁴⁰

This theory can be extended to a chronic life-limiting, highly symptomatic disease such as advanced HF. Physical, emotional, social or interpersonal, and spiritual or existential facets contribute to the experience of "total pain".⁴¹ Murray et al.⁴² described the end-of-life trajectories of social, psychological, and spiritual needs associated with patients with end-stage HF during their last year of life. The authors reported that in advanced HF, the decline in social and psychological well-being runs in parallel with physical deterioration and that spiritual distress fluctuates more than

other factors in advanced HF. Additionally, they concluded that spiritual distress is modulated by various other influences, including a perceived lack of understanding of these issues by health care professionals.

Physical pain is the most common form of pain. Chronic pain, which is frequent in HF, may be related to ongoing painful stimuli such as persistent inflammation or may be the result of the sensitization of central or peripheral neurons.⁴¹ It is deserving of note that the symptoms of pain may be an indirect indicator of the severity of congestive HF. The source of pain among patients with HF has been discussed in previous studies. Pain may result from edema or from impaired circulation to organs due to congestion and low cardiac output.³⁴ Other sources of pain in HF include constipation, visceral ischemia, musculoskeletal fatigue, mucositis, and ascites- which need specific consideration and management.²⁹

Many patients with HF suffer from pain in different locations of the body-including head, chest, stomach, back, extremities, and joints. Chest pain is more prevalent in HF than in non-HF cardiac patients.¹⁹ Udeoji et al.²⁵ found that 15% of their patients with stable chronic HF reported pain either in the chest, back, neck, and abdomen or in the extremities. About one-third of patients with HF experience chest pain.¹⁻³ The frequency of pain rises in patients with advanced HF. Goodlin et al.²² reported that the frequency of pain in their patients with advanced HF was 85% and that 40% of their patients suffered from pain at more than 1 site. In their study, severe or very severe pain was observed in 29% of the subjects with chest pain and in 39% of those with other sites of pain. Based on evidence, the presence of chest pain in patients with HF can lead to worse outcomes.⁴ Letterman et al.¹³ showed that chest pain in their series of patients with HF was associated with prolonged hospital stays, higher intensity care, and higher mortality. Moreover, results from the Carvedilol or Metoprolol European Trial (COMET) indicated that the presence of chest pain in patients with HF was significantly related to mortality and all-cause hospitalizations.⁸ Another study noted acute chest pain as a precipitant for admission in patients with new-onset HF.¹⁸ Interestingly, Goebel et al.¹⁹ found that headaches were more frequent among their non-HF cardiac patients than among their patients with HF and postulated that it might have been in consequence of the widespread use of nitrates to control angina and optimize preload. Still, headache tolerance may be observed in patients with long-term nitrate use.⁴²

Effect of Pain on Quality of Life in Patients with Heart Failure

Quality of life is a multidimensional subjective concept that is affected by many factors such as the physical, psychological, social, and economic status of patients and

their symptoms and limitations in daily life activities.⁵⁴ Pain can act both as a direct and as an indirect factor affecting quality of life in patients with HF.³⁰ Some studies have shown that pain is an important factor preventing patients from doing their daily activities, which indirectly lowers their quality of life.³⁰ In addition, pain is a contributing factor to nonadherence to medication and treatment, which worsens the symptoms of these patients and their quality of life.²⁸ The direct impact of pain is its effect on the physical and psychological well-being of the patient; it is a salient factor in determining the quality of life in chronic diseases.²⁸ The experience of pain also lessens cognitive functioning and increases anxiety, sleeplessness, depression, and hopelessness- thereby diminishing quality of life in these patients.⁶⁻⁸

Management of Pain in Patients with Heart Failure

The first step in managing pain in patients with HF is to identify the location, severity, and frequency of the pain as well as its possible causes and association with other problems.⁴² Pain from different sources should be treated by resolving the causative mechanism such as constipation, mucositis, and ascites.^{43, 44} As curative care options are limited for chronic pain caused by mechanisms unknown or not curable, palliation has become the priority in these patients.^{45, 46} Successful chronic pain management is defined as providing adequate analgesia without excessive adverse effects.⁴⁷ There have been different pharmaceutical therapies for treating pain in chronic diseases such as non-opioids like nonsteroidal anti-inflammatory (NSAID) drugs and opioids like codeine, morphine, and tramadol. Cardiovascular risks associated with the use of NSAIDs are important. NSAIDs, particularly cyclooxygenase 2 (COX-2) selective agents, have been reported to increase the risk of thrombotic events and myocardial infarction in patients with coronary artery disease and atherosclerosis. This led the American Heart Association to recommend that acetaminophen or non-acetylated salicylates be prescribed for patients with coronary artery disease.^{48, 49} The suitability of opioids for chronic non-cancer pain treatment is under debate. The efficacy of opioids in this clinical situation has only been reported in short-term trials, and evidence for their overall benefit in long-term therapy is missing.⁵⁰ Other drugs used in the treatment of chronic pain are antidepressants and anticonvulsants. The exact mechanism whereby antidepressants alleviate pain is not completely understood, but it is believed that they mediate the effect by inhibiting the neurotransmitter reuptake in the synaptic cleft.⁵¹ The safety of these drugs in patients with HF has yet to be fully investigated.⁵¹ Cannabinoids and triptans, which are also used for the management of chronic pain, are not safe in patients with coronary artery disease,



uncontrolled hypertension, and arrhythmias.^{52, 53} Because of the multiple interactions and adverse effects of these drugs in the management of chronic pain, there have been efforts to find novel ways for alleviating pain in these patients.⁴⁷ One of the novel methods for treating chronic pain is gene therapy, which utilizes viral vectors containing viral genome replaced with nucleic acid sequences encoding a promoter to drive gene expression as well as a transgene of interest such as an analgesic agent. A recent study in patients with terminal cancer demonstrated proof-of-concept for gene therapy in pain management. Physical training and exercise has been shown to significantly decrease circulating pro-inflammatory cytokines such as TNF- α and IL-6 and their soluble receptors (i.e., TNF-RI, TNF-RII, and IL-6R). These beneficial effects may be related to the training-induced improvement in the functional status of patients with HF—suggesting that persistent immune activation appears to be involved in impaired exercise capacity, which characterizes this syndrome.^{54, 55} As the different cytokines addressed in these studies play a role in generating pain in patients with HF,³³ it may be concluded that physical training and exercise can be of great help in alleviating pain in these patients. Other alternative self-treatments that can be employed by patients suffering from HF include walking, stretching, and using heat and cold on the zone of pain—which have yet to be comprehensively studied.⁵⁶

Conclusion

Although chronic pain is a common symptom in patients with HF and has a remarkable impact on various aspects of the management modalities of these patients, optimal control of pain is impossible. Further investigations are needed to find a safe and efficacious way for controlling pain in patients with HF.

References

1. Roger VL. Epidemiology of heart failure. *Circ Res* 2013;113:646-659.
2. Johnson MJ. Management of end stage cardiac failure. *Postgrad Med J* 2007;83:395-401.
3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiger A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14:803-869.
4. Blinderman CD, Homel P, Billings JA, Portenoy RK, Tennstedt SL. Symptom distress and quality of life in patients with advanced congestive heart failure. *J Pain Symptom Manage* 2008;35:594-603.
5. Cotter G, Milo O, Davison BA. Increased mortality after an acute heart failure episode: new pathophysiological insights from the RELAX-AHF study and beyond. *Curr Heart Fail Rep* 2014;11:19-30.
6. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation; endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154-235.
7. Nordgren L, Sörensen S. Symptoms experienced in the last six months of life in patients with end-stage heart failure. *Eur J Cardiovasc Nurs* 2003;2:213-217.
8. Ekman I, Cleland JG, Swedberg K, Charlesworth A, Metra M, Poole-Wilson PA. Symptoms in patients with heart failure are prognostic predictors: insights from COMET. *J Card Fail* 2005;11:288-292.
9. Zambroski CH, Moser DK, Bhat G, Ziegler C. Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. *Eur J Cardiovasc Nurs* 2005;4:198-206.
10. Godfrey C, Harrison MB, Medves J, Tranmer JE. The symptom of pain with heart failure: a systematic review. *J Card Fail* 2006;12:307-313.
11. McCaffery M. Pain management. In: McCaffery M, Pasero C, eds. *Pain: Clinical Manual*. 2nd ed. Finland: Mosby Incorporated; 1999. p. 125-135.
12. Sullivan M, Levy WC, Russo JE, Spertus JA. Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. *J Card Fail* 2004;10:390-396.
13. Lettman NA, Sites FD, Shofer FS, Hollander JE. Congestive heart failure patients with chest pain: incidence and predictors of acute coronary syndrome. *Acad Emerg Med* 2002;9:903-909.
14. Lip G, Zarifis J, Beavers DG. Acute admissions with heart failure to a district general hospital serving a multiracial population. *Int J Clin Pract* 1997;51:223-227.
15. Whelan CT, Jin L, Meltzer D. Pain and satisfaction with pain control in hospitalized medical patients: no such thing as low risk. *Arch Intern Med* 2004;164:175-180.
16. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA* 1998;280:147-151.
17. Godfrey CM, Harrison MB, Friedberg E, Medves JM, Tranmer JE. The symptom of pain in individuals recently hospitalized for heart failure. *J Cardiovasc Nurs* 2007;22:368-374.
18. Chin MH, Goldman L. Factors contributing to the hospitalization of patients with congestive heart failure. *Am J Public Health*

- 1997;87:643-648.
19. Goebel JR, Doering LV, Evangelista LS, Nyamathi AM, Maliski SL, Asch SM, Sherbourne CD, Shugarman LR, Lanto AB, Cohen A, Lorenz KA. A comparative study of pain in heart failure and non-heart failure veterans. *J Card Fail* 2009;15:24-30.
 20. Conley S, Feder S, Redeker NS. The relationship between pain, fatigue, depression and functional performance in stable heart failure. *Heart Lung* 2015;44:107-112.
 21. Evangelista LS, Berg J, Dracup K. Relationship between psychosocial variables and compliance in patients with heart failure. *Heart Lung* 2001;30:294-301.
 22. Goodlin SJ, Wingate S, Albert NM, Pressler SJ, Houser J, Kwon J, Chiong J, Storey CP, Quill T, Teerlink JR; PAIN-HF Investigators. Investigating pain in heart failure patients: the pain assessment, incidence, and nature in heart failure (PAIN-HF) study. *J Card Fail* 2012;18:776-783.
 23. Rustøen T, Stubhaug A, Eidsmo I, Westheim A, Paul SM, Miaskowski C. Pain and quality of life in hospitalized patients with heart failure. *J Pain Symptom Manage* 2008;36:497-504.
 24. Shah AB, Udeoji DU, Baraghoush A, Bharadwaj P, Yennurajalingam S, Schwarz ER. An evaluation of the prevalence and severity of pain and other symptoms in acute decompensated heart failure. *J Palliat Med* 2013;16:87-90.
 25. Udeoji DU, Shah AB, Bharadwaj P, Katsiyannis P, Schwarz ER. Evaluation of the prevalence and severity of pain in patients with stable chronic heart failure. *World J Cardiol* 2012;4:250-255.
 26. Gan Q, Zhang FR, Zhou QF, Dai LY, Liu YH, Chai XC, Wu F, Shen WF. Clinical significance of pain in patients with chronic heart failure. *Chin Med J (Engl)* 2012;125:3223-3227.
 27. Pantilat SZ, O'Riordan DL, Rathfon MA, Dracup KA, De Marco T. Etiology of pain and its association with quality of life among patients with heart failure. *J Palliat Med* 2016;19:1254-1259.
 28. Evangelista LS, Sackett E, Dracup K. Pain and heart failure: unrecognized and untreated. *Eur J Cardiovasc Nurs* 2009;8:169-173.
 29. Bekelman DB, Havranek EP, Becker DM, Kutner JS, Peterson PN, Wittstein IS, Gottlieb SH, Yamashita TE, Fairclough DL, Dy SM. Symptoms, depression, and quality of life in patients with heart failure. *J Card Fail* 2007;13:643-648.
 30. Levenson JW, McCarthy EP, Lynn J, Davis RB, Phillips RS. The last six months of life for patients with congestive heart failure. *J Am Geriatr Soc* 2000;48:S101-109.
 31. Desbiens NA, Mueller-Rizner N, Connors AF, Wenger NS. The relationship of nausea and dyspnea to pain in seriously ill patients. *Pain* 1997;71:149-156.
 32. Desbiens NA, Wu AW, Alzola C, Mueller-Rizner N, Wenger NS, Connors AF, Jr, Lynn J, Phillips RS. Pain during hospitalization is associated with continued pain six months later in survivors of serious illness. The SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Am J Med* 1997;102:269-276.
 33. Desbiens NA, Wu AW, Broste SK, Wenger NS, Connors AF, Jr, Lynn J, Yasui Y, Phillips RS, Fulkerson W. Pain and satisfaction with pain control in seriously ill hospitalized adults: findings from the SUPPORT research investigations. For the SUPPORT investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *Crit Care Med* 1996;24:1953-1961.
 34. Goodlin SJ, Wingate S, Pressler SJ, Teerlink JR, Storey CP. Investigating pain in heart failure patients: rationale and design of the Pain Assessment, Incidence & Nature in Heart Failure (PAIN-HF) study. *J Card Fail* 2008;14:276-282.
 35. Goodlin SJ. Care of the older patient with pain. *Curr Pain Headache Rep* 2004;8:277-280.
 36. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, Shao Y, Hu X. Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis. *Prev Med* 2014;63:36-42.
 37. Schäfers M, Sommer C, Geis C, Hagenacker T, Vandenabeele P, Sorkin LS. Selective stimulation of either tumor necrosis factor receptor differentially induces pain behavior in vivo and ectopic activity in sensory neurons in vitro. *Neuroscience* 2008;157:414-423.
 38. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, Liu Y, Hoffmann U, Bauer DC, Newman AB, Kritchevsky SB, Harris TB, Butler J; Health ABC Study Investigators. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol* 2010;55:2129-2137.
 39. Kleinbongard P, Heusch G, Schulz R. TNFalpha in atherosclerosis, myocardial ischemia/reperfusion and heart failure. *Pharmacol Ther* 2010;127:295-314.
 40. Saunders DC, Baines M. Living with Dying. In: Saunders DC, ed. *Living with Dying: The Management of Terminal Disease*. 2nd ed. New York: Oxford University Press; 1989. p. 110-114.
 41. Light-McGroary K, Goodlin SJ. The challenges of understanding and managing pain in the heart failure patient. *Curr Opin Support Palliat Care* 2013;7:14-20.
 42. Murray SA, Kendall M, Grant E, Boyd K, Barclay S, Sheikh A. Patterns of social, psychological, and spiritual decline toward the end of life in lung cancer and heart failure. *J Pain Symptom Manage* 2007;34:393-402.
 43. Anderson H, Ward C, Eardley A, Gomm SA, Connolly M, Copping T, Corgie D, Williams JL, Makin WP. The concerns of patients under palliative care and a heart failure clinic are not being met. *Palliat Med* 2001;15:279-286.
 44. Goebel JR, Doering LV, Shugarman LR, Asch SM, Sherbourne CD, Lanto AB, Evangelista LS, Nyamathi AM, Maliski SL, Lorenz KA. Heart failure: the hidden problem of pain. *J Pain Symptom Manage* 2009;38:698-707.
 45. Christiansen I, Iversen HK, Olesen J. Headache characteristics during the development of tolerance to nitrates: pathophysiological implications. *Cephalalgia* 2000;20:437-444.
 46. Hauptman PJ, Goodlin SJ, Lopatin M, Costanzo MR, Fonarow GC, Yancy CW. Characteristics of patients hospitalized with acute decompensated heart failure who are referred for hospice care. *Arch Intern Med* 2007;167:1990-1997.
 47. Kapur BM, Lala PK, Shaw JL. Pharmacogenetics of chronic pain management. *Clin Biochem* 2014;47:1169-1187.
 48. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest* 2006;116:4-15.
 49. Mukherjee D. Does a coxib-associated thrombotic risk limit the clinical use of the compounds as analgesic anti-inflammatory drugs? Arguments in favor. *Thromb Haemost* 2006;96:407-412.
 50. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, Sehgal N, Shah R, Benyamin R, Vallejo R, Fellows B, Christo PJ. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011;14:91-121.
 51. Sansone RA, Sansone LA. Pain, pain, go away: antidepressants and pain management. *Psychiatry (Edgmont)* 2008;5:16-19.
 52. Loder E. Triptan therapy in migraine. *N Engl J Med* 2010;363:63-70.
 53. Clark AJ, Lynch ME, Ware M, Beaulieu P, McGilveray IJ, Gourlay D. Guidelines for the use of cannabinoid compounds in chronic pain. *Pain Res Manag* 2005;10 Suppl A:44A-46A.
 54. Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, Kempf W, Schubert A, Schuler G, Hambrecht R. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol* 2003;42:861-868.
 55. Adamopoulos S, Parissis J, Karatzas D, Kroupis C, Georgiadis M, Karavolias G, Paraskevaidis J, Koniavitou K, Coats AJ, Kremastinos DT. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fasligand system in patients with chronic heart failure. *J Am Coll Cardiol* 2002;39:653-663.
 56. McDonald DD, Soutar C, Chan MA, Afriyie A. A closer look: alternative pain management practices by heart failure patients with chronic pain. *Heart Lung* 2015;44:395-399.