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Society Guidelines

The 2011 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Sleep Apnea, Renal Dysfunction, Mechanical Circulatory Support, and Palliative Care

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ABSTRACT

The 2011 Canadian Cardiovascular Society Heart Failure (HF) Guidelines Focused Update reviews the recently published clinical trials that

RÉSUMÉ

La mise à jour 2011 des lignes directrices de l'insuffisance cardiaque (IC) de la Société canadienne de cardiologie revoit les récents

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The disclosure information of the authors and reviewers is available from the CCS on the following websites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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will potentially impact on management. Also reviewed is the less studied but clinically important area of sleep apnea. Finally, patients with advanced HF represent a group of patients who pose major difficulties to clinicians. Advanced HF therefore is examined from the perspectives of HF complicated by renal failure, the role of palliative care, and the role of mechanical circulatory support (MCS). All of these topics are reviewed from a perspective of practical applications. Important new studies have demonstrated in less symptomatic HF patients that cardiac resynchronization therapy will be of benefit. As well, aldosterone receptor antagonists can be used with benefit in less symptomatic HF patients. The important role of palliative care and the need to address end-of-life issues in advanced HF are emphasized. Physicians need to be aware of the possibility of sleep apnea complicating the course of HF and the role of a sleep study for the proper assessment and management of the conditon. Patients with either acute severe or chronic advanced HF with otherwise good life expectancy should be referred to a cardiac centre capable of providing MCS. Furthermore, patients awaiting heart transplantation who deteriorate or are otherwise not likely to survive until a donor organ is found should be referred for MCS.

essais cliniques publiés qui auront potentiellement une incidence sur la gestion. L'apnée du sommeil, qui est un domaine cliniquement important, mais peu étudié, a aussi été revue. Finalement, les patients avec une IC avancée représentent un groupe de patients qui posent des difficultés majeures aux cliniciens. Par conséquent, l'IC avancée est analysée selon la perspective d'une IC compliquée par une insuffisance rénale, le rôle des soins palliatifs et le rôle de l'assistance circulatoire mécanique (ACM). Tous ces sujets sont analysés dans une perspective d'applications pratiques. D'importantes nouvelles études ont démontré que chez les patients avec une IC moins symptomatique la thérapie de resynchronisation cardiaque sera bénéfique. Aussi, les antagonistes des récepteurs de l'aldostérone peuvent être utilisés de manière bénéfique chez les patients avec une IC moins symptomatique. Le rôle important des soins palliatifs et le besoin de tenir compte des enjeux de fin de vie dans l'IC avancée sont mis de l'avant. Les médecins ont besoin de ne pas ignorer la possibilité d'une apnée du sommeil compliquant le cours de l'IC et le rôle de l'étude du sommeil pour l'évaluation et la gestion appropriées de la condition. Les patients qui ont soit une IC aiguë avancée ou une IC chronique sévère mais une bonne espérance de vie devraient être dirigés à un centre cardiaque en mesure de fournir une ACM. En plus, les patients en attente d'une transplantation cardiaque qui se détériorent ou qui ne sont pas autrement susceptibles de survivre jusqu'à ce qu'un organe de donneur soit trouvé devraient être dirigés pour une ACM.

The Canadian Cardiovascular Society (CCS) has been publishing the Heart Failure (HF) Guidelines since 2006.[1] This is part of a commitment to a multiyear, closed-loop initiative to provide support for the best practice of HF management. The CCS has also implemented the National HF Workshop Initiative; a series of HF workshops across the country initiated to discuss how to implement the guidelines and to identify additional challenges facing physicians and other health care providers in their daily management of HF patients. Feedback from these sessions, together with specific solicited input from key stakeholders, led to other important topics covered in the 2007,[2] 2008,[3] 2009,[4] and 2010[5] updates. This program of annual updates has produced a series of evidence-based papers outlining the management of HF.

The constitution and roles of primary and secondary panels, systematic review strategy, and methods for formulating the recommendations are described in more detail on the CCS HF Consensus Conference Program website (www.hfcc.ca).

The objectives of the 2011 CCS HF Consensus Update were to provide recommendations and practical tips in the areas of (1) recently published significant clinical studies, (2) HF complicated by renal failure, (3) management of sleep apnea, (4) palliative care, and (5) the use of mechanical circulatory support (MCS).

The recommendations this year follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[6] The GRADE system classifies the quality of evidence as High (further research very unlikely to change confidence in the estimate of effect), Moderate (further research likely to have an important impact on confidence in the estimate of effect and may change the estimate), Low (further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate), and Very Low (estimate of effect very uncertain). The GRADE system offers 2 grades of recommendations: "strong" (desirable effects clearly outweigh undesirable effects, or clearly do not) and "weak." When tradeoffs are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced, weak recommendations become mandatory.[6]

Important New Clinical Trials That Would Likely Change the Standard of Care in HF

Should cardiac resynchronization therapy be extended to patients with milder HF?

Cardiac resynchronization therapy (CRT) progressively improves left ventricular (LV) structure and function, raising the possibility that CRT may delay disease progression in patients with less severe symptoms.[7] Two small studies in New York Heart Association (NYHA) class II patients found improvements in cardiac remodelling.[8,9] More recently, larger studies (reviewed later) have provided further evidence to support the use of CRT in less symptomatic patients.[10-13]

In the Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) trial, the effects of CRT therapy (with implantable cardioverter-defibrillator [ICD] in most patients) were assessed in 610 NYHA I or II HF patients.[10] The primary end point of HF clinical composite (improved, unchanged, or worsened) was not significantly different between groups. For the secondary outcomes, CRT-on compared to CRT-off showed a significantly greater reduction in LV end-systolic volume index and delay in time-to-first HF hospitalization (hazard ratio [HR] 0.47; $P = 0.03$).

The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) was designed to determine whether prophylactic CRT in combination with an ICD (CRT-ICD) would reduce the risk of death or nonfatal HF events in NYHA I or II patients with an LV ejection fraction (EF) $\leq$ 30%, and QRS duration $\geq$130 ms, compared with ICD alone.[11] There was a significant 34% ($P = 0.001$) reduction in the primary outcome in the CRT-ICD group (Table 1). The benefit of CRT-ICD was similar in patients with ischemic or nonischemic etiologies (Table 1). The improvement in the primary endpoint was due to a 41% ($P < 0.001$) decrease in nonfatal HF in the CRT-ICD group; there was no significant effect on mortality. Similar to the REVERSE trial, there were significant

Table 1. Risk of death or heart failure (HF) in the MADIT-CRT study

Variable	ICD-only group	CRT-ICD group	HR (95% CI)	*P* value
All patients	731	1089		
Death or HF	185 (25.3%)	187 (17.2%)	0.66 (0.52-0.84)	<0.0001
HF only	167 (22.8%)	151 (13.9%)	0.59 (0.47-0.74)	<0.001
Death at any time	53 (7.3%)	74 (6.8%)	1.00 (0.69-1.44)	0.99
Patients with ischemic cardiomyopathy (NYHA class I or II)	401	598		
Death or HF	117 (29.2%)	122 (20.4%)	0.67 (0.52-0.88)	0.003
HF only	105 (26.2%)	96 (16.1%)	0.58 (0.44-0.78)	<0.001
Patients with nonischemic cardiomyopathy (NYHA class II)	330	491		
Death or HF	68 (20.6%)	65 (13.2%)	0.62 (0.44-0.89)	0.01
HF only	62 (18.8%)	55 (11.2%)	0.59 (0.41-0.87)	0.01

CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; NYHA, New York Heart Association.

improvements in cardiac volumes with CRT-ICD and these improvements were associated with a significant reduction in risk.

The Resynchronization-Defibrillation for Ambulatory HF Trial (RAFT)[12] recruited almost 2000 patients and the average follow-up was longer (40 months) compared to MADIT-CRT (28.8 months).[11] Initially, NYHA II or III HF patients were recruited, but as new evidence showed benefit for NYHA III patients, the study changed enrolment criteria to recruit only NYHA II patients, resulting in 80% of patients with NYHA II symptoms. Other important inclusion criteria were optimal medical management, LVEF ≤ 30%, QRS duration ≥120 ms, or paced QRS duration ≥200 ms. The primary outcome of any-cause death or HF hospitalization was reduced 25% ($P < 0.001$) in the ICD-CRT group compared to the ICD group (Table 2). There was a 25% reduction of death ($P = 0.003$) and a 32% reduction ($P < 0.001$) of HF hospitalizations with ICD-CRT (Table 2). There was no interaction between treatment and cause of HF (ischemic vs nonischemic).

These recently published studies suggest that adding CRT in combination with ICD therapy, on top of optimal medical therapy in less symptomatic HF patients (NYHA II), results in reduction in mortality and morbidity. The subgroup analyses of both MADIT-CRT and RAFT used a cut-point of QRS duration ≥ 150 ms, the remarkable consistency in terms of more benefit in patients with QRS duration ≥ 150 ms indicate that the benefit increases with increasing QRS duration in this patient population with milder symptoms.

RECOMMENDATION

We recommend the use of CRT in combination with an ICD for HF patients on optimal medical therapy with NYHA II HF symptoms, LVEF ≤ 30%, and QRS duration ≥ 150 ms (Strong Recommendation, High-Quality Evidence).

Practical tip. The use of 150 ms as a cut-point for QRS duration was based on a subgroup analysis of the data. The MADIT-CRT study included patients with QRS duration ≥130 ms, while RAFT included patients with QRS duration ≥120 ms. Therefore in practice the selection of patients should be individualized and based on risk features. For example, patients with NYHA II symptoms with LVEF ≤ 20% should likely be considered for treatment even if their QRS durations are slightly below 150 ms but wider than 120 ms.

Should aldosterone receptor blockade be extended to patients with milder HF?

Activation of the mineralocorticoid receptors by aldosterone exerts deleterious effects in patients with cardiovascular disease (CVD).[14] A recent systematic review found that aldosterone blockade in a clinically heterogeneous group of participants with HF and post myocardial infarction resulted in a significant 20% reduction in all-cause mortality.[15] The recently published Epler-

Table 2. Risk of death or hospitalization for heart failure (HF) in the RAFT study

Outcome	ICD (N = 904)	ICD-CRT (N = 894)	Hazard ratio (95% CI)	*P* value
All patients				
Primary outcome				
Death or hospitalization for HF	363 (40.3%)	297 (33.2%)	0.75 (0.64-0.87)	<0.001
Secondary outcomes				
Death from any cause	236 (26.1%)	186 (20.8%)	0.75 (0.62-0.91)	0.003
Hospitalization for HF	236 (26.1%)	174 (19.5%)	0.68 (0.56-0.83)	<0.001
Patients in NYHA class II				
No. of patients	730	708		
Primary outcome				
Death or hospitalization for HF	253 (34.7%)	193 (27.3%)	0.73 (0.61-0.88)	0.001
Secondary outcomes				
Death from any cause	154 (21.1%)	110 (15.5%)	0.71 (0.56-0.91)	0.006
Hospitalization for HF	159 (21.8%)	115 (16.2%)	0.70 (0.55-0.89)	0.003

CI, confidence interval; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; RAFT, Resynchronization-Defibrillation for Ambulatory HF Trial.

Table 3. Primary outcome and key secondary outcomes in the EMPHASIS-HF study

Outcome	Eplerenone (N = 1364)	Placebo (N = 1373)	Adjusted HR (95% CI)	Adjusted *P* value
Primary outcome				
Death or hospitalization for HF	249 (18.3%)	356 (25.9%)	0.63 (0.54-0.74)	<0.001
Prespecified adjudicated secondary outcomes				
Death from any cause	171 (12.5%)	213 (15.5%)	0.76 (0.62-0.93)	0.008
Death from cardiovascular causes	147 (10.8%)	185 (13.5%)	0.76 (0.61-0.94)	0.01
Hospitalization for any reason	408 (29.9%)	491 (35.8%)	0.77 (0.67-0.88)	<0.001
Hospitalization for HF	164 (12.0%)	253 (18.4%)	0.58 (0.47-0.70)	<0.001

CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF, heart failure; HR, hazard ratio.

enone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) expands the use of aldosterone receptor antagonists in HF patients.[16]

EMPHASIS-HF examined the effects of eplerenone on clinical outcomes in patients ≥ 55 years old, with NYHA II symptoms, LVEF ≤ 30% (if > 30%-35%, a QRS duration of >130 ms), treated with an angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin receptor blocker, and β-blockers (if indicated). Randomized patients were within 6 months of hospitalization for CVD reasons; if > 6 months for hospitalization, brain natriuretic peptide (BNP) needed to be ≥ 250 pg/mL or N-terminal (NT)-pro-BNP ≥ 500 pg/mL in men and ≥ 750 pg/mL in women. There were > 2700 patients with a median follow-up of 21 months. The primary composite outcome (death from CVD causes or a first hospitalization for HF) was reduced by 37% with eplerenone (Table 3). Eplerenone also reduced death from any cause, hospitalization for any reason, HF hospitalization, and CVD deaths. The effect of eplerenone on the primary outcome was consistent across prespecified subgroups. Although eplerenone reduced clinical events in patients with milder symptoms of HF, the tight inclusion criteria limit generalizability of the findings to all patients with HF.

RECOMMENDATION

We recommend that an aldosterone receptor blocking agent such as eplerenone be considered for patients with mild to moderate (NYHA II) HF, aged > 55 years with LV systolic dysfunction (LVEF ≤ 30%, or if LVEF > 30% and ≤ 35% with QRS duration > 130 ms), and recent hospitalization for CVD or elevated BNP/NT-pro-BNP levels, who are on standard HF therapy (Strong Recommendation, High-Quality Evidence).

Practical tip. Key exclusion criteria in the EMPHASIS study included a serum potassium level > 5.0 mmol/L and an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2. Therefore, it is important to monitor these laboratory variables and to not use eplerenone in those patients who exceed these levels for potassium and eGFR.

Does lowering heart rate improve clinical outcomes in chronic HF?

Resting heart rate independently predicts CVD events, including HF hospitalization.[17,18] Systematic reviews have demonstrated that a major contributor to the benefits of β-blocker therapy may be their rate-lowering effect.[19,20] Despite their benefits, these agents are generally underused and underdosed.[21,22] If appropriately optimized, β-blockade does not reduce heart rate; further therapy that would lower heart rate is warranted. Ivabradine reduces heart rate by specific inhibition of the I_f current, which is important for sinoatrial node pacemaking.[23]

The Systolic Heart Failure Treatment with I_f inhibitor ivabradine Trial (SHIFT) examined the effect of ivabradine in patients with moderate to severe HF.[24] The inclusion criteria were symptomatic HF for ≥ 4 weeks, resting heart rate ≥ 70 bpm, LVEF ≤ 35%, and HF admission within 12 months. The primary endpoint was a composite of CVD death or HF admission. Heart rate in the ivabradine group was lower than placebo by 9.1 bpm and 8.1 bpm at 1 year and at the end of the study, respectively. Ivabradine produced a significant 18% reduction in the primary endpoint (Table 4). The effects were driven mainly by hospital admissions for worsening HF and deaths due to HF. Ivabradine did not reduce all-cause mortality or CVD mortality (Table 4). Among 10% of patients not on β-blocker therapy, there was a larger reduction in the primary endpoint (HR 0.68; 95% CI, 0.52-0.88).

The results of this trial contrast with those of the morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with CAD and left ventricULar dysfunction (BEAUTIFUL) study of > 10,000 patients with asymptomatic LV systolic dysfunction due to ischemic heart disease.[17,25] The BEAUTIFUL trial demonstrated a nonsignificant trend toward the reduction of the primary endpoint. The mean heart rate in BEAUTIFUL was lower than that in SHIFT. In BEAUTIFUL, the group with a resting heart rate ≥70 bpm showed a significant reduction in myocardial infarction and CVD death consistent with the hypothesis that heart rate is related to outcome.

Practical tip. At present, ivabradine has not yet been approved for clinical use in Canada. When ivabradine does become available, the results of SHIFT will likely support the use of ivabradine in patients with moderate to severe HF on optimum medical therapy including β-blockade with LVEF ≤ 35% and resting heart rate ≥ 70 bpm.

Important Clinical Trials That Do Not Yet Change Standard of Care

Should we routinely measure natriuretic peptide in patients with chronic HF?

The use of natriuretic peptides (BNP/NT-pro-BNP) was reviewed in previous CCS HF Guidelines.[2,4] Since then, the

Table 4. Effects of ivabradine on primary and major secondary endpoints in the SHIFT study

	Ivabradine group (n = 3241)	Placebo group (n = 3264)	HR (95% CI)	*P* value
Primary endpoint				
Cardiovascular death or hospital admission for worsening HF	793 (25%)	937 (29%)	0.82 (0.75-0.90)	<0.0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0.90 (0.80-1.02)	0.092
Cardiovascular mortality	449 (14%)	491 (15%)	0.91 (0.80-1.03)	0.128
Death from HF	113 (3%)	151 (5%)	0.74 (0.58-0.94)	0.014
Other endpoints				
Hospital admission for worsening HF	514 (16%)	672 (21%)	0.74 (0.66-0.83)	<0.0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0.85 (0.78-0.92)	0.0002

CI, confidence interval; HF, heart failure; HR, hazard ratio; SHIFT, Systolic Heart Failure Treatment with I_f inhibitor ivabradine Trial.

results of several studies addressing natriuretic peptide (NP) testing in chronic HF have been published.

The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) multicentre study randomized 499 patients ≥ 60 years old to guideline-based therapy or intensified NT-pro-BNP-guided therapy.[26] The primary outcome, 18-month survival free of all-cause hospitalizations, was similar between groups and there was no difference in quality of life. The secondary outcome (survival free of hospitalization for HF) was higher in the NT-pro-BNP group. In patients aged 60 to < 75 years, NT-pro-BNP-guided therapy improved outcomes but not in patients ≥ 75 years old.

The NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trial compared the effects of NT-pro-BNP-guided therapy (HG) with intensive standardized clinical management (CG) and usual care (UC) in 364 patients.[27] In the CG group, a HF score ≥ 2.0 was used to trigger optimization of therapy. For the HG group, NT-pro-BNP >150 pmol/L and/or HF score ≥ 2.0 triggered optimization of drugs. One-year mortality was significantly less in both the HG (9.1%) and CG (9.1%) groups compared to the UC group (18.9%). In patients aged ≤ 75 years, 3-year mortality was lower in the HG group compared to CG and UC groups.

The Can Pro-brain-natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality (PRIMA) study examined whether treatment of HF guided by an individualized target NT-pro-BNP level improves outcome.[28] A total of 345 hospitalized HF patients with elevated NT-pro-BNP levels at admission were included. After discharge, patients were randomized to either clinically guided outpatient management or management guided by an individually set NT-pro-BNP defined by the lowest level at discharge or 2 weeks thereafter. There was no difference in the primary outcome for the number of days alive outside the hospital between the NT-pro-BNP-guided and the clinically guided groups.

Since the 2009 Guidelines, the role of NP monitoring in the management of patients with chronic HF remains undefined. The results point to possible value in selected patiens such as those < 75 years of age. However, these impressions may change when ongoing studies like EX-IMPROVE-CHF and PROTECT are published.

What Should You Do When HF Is Complicated by Renal Failure?

Cardiorenal syndrome

Cardiac and renal dysfunction often occur in concert with hemodynamic, neurohormonal, vascular, and hematologic consequences. Previously, renal dysfunction was thought to represent merely a comorbidity in patients with advanced HF. It is increasingly recognized that cardiac and renal interaction is complex. The cardiorenal syndrome (CRS) refers to interactions in which renal dysfunction and HF interact and mutually reinforce each other.[29] Mechanistic hypotheses are discussed elsewhere.[29,30] Both elevated intra-abdominal pressure and central venous pressure are linked to rising serum creatinine levels.[31,32]

A meta-analysis of observational studies confirms that HF patients with moderate to severe renal dysfunction have a > 2-fold increase in relative mortality risk.[33] The presence of HF in a hemodialysis population portends a poor prognosis with mean survival of < 36 months.[34]

Creatinine clearance calculated by Cockcroft and Gault[35] or according to the MDRD formula[36] estimates the GFR, with normal renal function indicated by a GFR ≥ 90 mL/min/1.73 m^2, mild renal dysfunction by a GFR of 60 to 89 mL/min/1.73 m^2, moderate renal dysfunction by a GFR ≥ 30 to 59 mL/min/1.73 m^2, severe renal dysfunction by a GFR of 15 to 29 mL/min/1.73 m^2, and end-stage renal dysfunction <15 mL/min/1.73 m^2. Standardized and validated criteria may be useful to estimate acute changes in renal function at the bedside for patients with acute decompensated HF (ADHF) when renal injury is a possibility. The Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) criteria have been validated and are based on a creatinine level that is 1.5, 2, or 3 times the baseline creatinine with a concurrent drop in urine output over 6, 12, or 24 hours.[37] It is important to recognize that markers used in the assessment of HF including BNP and NT-pro-BNP may need to be interpreted with caution in the presence of acute renal failure or end-stage renal disease.

Supplemental Table S1 provides guidance on assessment and options when assessing the CRS and the need for further intervention, including diuretics, ultrafiltration (UF), or dialysis.

RECOMMENDATION

We recommend that patients with the CRS should be managed by a multispecialty team with experience and expertise (Strong Recommendation, Low-Quality Evidence).

Practical tip. Careful assessment of all clinical indicators of fluid status is mandatory as changes in body weight may relate to changes in concurrent changes in fluid status or to muscle or fat content.

When evaluating patients, attention should be paid to the evolution of symptoms, renal function, body weight, and fluid status to aid management.

Overaggressive fluid removal should be avoided, especially in advanced biventricular HF and severe chronic kidney disease.

Role of hemodialysis

In critically ill HF patients, hemodynamic stress, metabolic changes, and electrolyte shifts often occur in patients on hemodialysis and may be poorly tolerated. Dialysis should be considered in HF patients with signs and symptoms of complications of renal failure (Supplemental Table S1).[38] The urgency should be discussed with a nephrologist with experience in performing hemodialysis on HF patients.

Before initiating dialysis, clinicians should be aware of the poor prognosis of HF patients and end-stage renal disease (see section on palliative care). Once initiated, clinicians and patients may have difficulty accepting the need to discontinue or continue dialysis. Common complications associated with dialysis include dehydration and electrolyte imbalance, which may lead to angina, hypotension, or arrhythmias if left untreated. A reduction in medical therapy may be necessary for effective hemodialysis to occur, and there should be caution when reintroducing these at a later time.

Medications specific to HF should be continued when possible. A randomized controlled trial of carvedilol in 114 hemodialysis patients with a low LVEF and HF symptoms demonstrated a significant reduction in mortality or hospitalization over 2 years and improvement in NYHA and LV remodelling.[39] Cohort data suggest that ACE inhibitors are associated with a reduction in all-cause mortality.[40] A single randomized controlled trial of 397 high-risk patients without HF on hemodialysis showed a trend toward a lower event rate with the use of fosinopril.[41] Similarly, angiotensin II receptor blockers (ARBs) have been tested in an open-label trial in hemodialysis patients[42] and were not found to reduce clinical events. One randomized trial of 332 HF patients on an ACE inhibitor and hemodialysis demonstrated a significant all-cause mortality reduction over 3 years with the ARB telmisartan but with significantly more hypotension and dropouts in the treatment arm.[43] These results do not alter prior recommendations on combination therapy with ACE and an ARB. Aldosterone blockade has been evaluated in 3 small cohorts for safety[44-46] and 1 small randomized controlled trial of 16 HF patients without significant benefits.[47] There are limited safety data and no efficacy data favouring digoxin for HF patients on hemodialysis.

RECOMMENDATION

In patients already on dialysis, we recommend to initiate or continue the use of ACE inhibitors and β-blockers in patients with HF and an LVEF $<$ 35% (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. The dosing or timing of medications may need to be altered to accommodate effective hemodialysis and optimize pharmacokinetics.

Role of renal transplantation

Renal transplant is an option for selected candidates with HF according to internationally accepted guidelines.[48] Three cohort studies have highlighted the importance of the cardiorenal interaction in patients who have undergone renal transplantation and subsequently had improvement in symptoms, LV function, and remodelling.[49-51] Postoperative adverse cardiac events were low ($<$5%) in these patient cohorts.

RECOMMENDATION

We suggest that in low LVEF HF patients, HF should not preclude renal transplant candidacy (Weak Recommendation, Moderate-Quality Evidence).

Role of ultrafiltration

Diuretic therapy is the mainstay for relief of volume overload for ADHF.[52] However, evidence-based data are sparse and diuretics have adverse effects such as activation of the neurohormonal cascade, electrolyte depletion, and renal injury.[53,54] While diuretic administration results in hypotonic urine, ultrafiltration (UF) leads to the production of isonatremic and iso-osmolar urine.

Trials in ultrafiltration

The multicentre randomized controlled Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial assessed the feasibility, safety, and efficacy of early UF vs usual care in the management of ADHF.[55] Early UF resulted in a trend toward greater weight loss and fluid removal at 24 hours. UF was well tolerated and the median volume of ultrafiltrate removed during a single 8-hour course of UF was 3213 mL. Dyspnea and HF symptoms were significantly improved in the UF group at 48 hours.

In the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial, early UF was compared to standard intravenous diuretic therapy in ADHF patients.[56] UF produced greater weight loss and net fluid loss over 48 hours but no difference in dyspnea scores, creatinine level, or length of stay. There was an associated decrease in HF rehospitalization at 90 days but other important clinical outcomes were not affected. The studies on UF were not powered to address major clinical outcomes; and no long-term evaluation ($>$ 90 days) of

the impact on HF or all-cause hospitalizations has been performed.

Safety of ultrafiltration

The potential risks associated with UF include hypotension, bleeding, hemolysis, catheter-related complications, allergic reactions, and air emboli.[57] Currently, patients receiving UF need to receive systemic anticoagulation, placing an additional risk of systemic bleeding. Estimates regarding the safety of UF based on the published literature are from small randomized controlled trials and cannot be readily extrapolated to a broader population in centres without experience and expertise in UF. To date, there is no evidence to support the notion that use of UF may be a renoprotective strategy.

RECOMMENDATION

We suggest that in patients with ADHF and diuretic resistance, UF may be considered for volume management and is to be performed in centres by clinicians with experience and expertise in its use (Weak Recommendation, Low-Quality Evidence).

How Do You Assess and Manage Sleep Apnea in HF Patients?

What is sleep apnea?

Apnea is defined as the cessation of airflow for >10 seconds; hypopnea is a > 50% airflow reduction without complete cessation. Obstructive sleep apnea (OSA) and hypopnea result from complete or partial collapse of the pharynx; central sleep apnea (CSA) results from withdrawal of central drive to the respiratory muscles. The apnea-hypopnea index (AHI) quantifies the frequency of apneas and hypopneas per hour of sleep.[38,58]

The diminished pharyngeal dilator muscle tone at the onset of sleep leading to OSA is augmented by local adiposity and rostral fluid shift.[59,60,61] The cyclic oscillations of hyperpnea followed by apnea characteristic of CSA commence with lung congestion- or arousal-initiated hyperpnea. $Paco_2$ is driven below the patient's apneic threshold, causing withdrawal of central drive to the muscles of respiration, and breathing does not resume until $Paco_2$ overshoots, stimulating another cycle of hyperpnea followed by apnea. Propensity to both OSA and CSA can be compounded by unstable ventilatory control, secondary to increased chemoreceptor reflex gain,[61] which may be present in up to 40% of patients with HF.[62,63]

OSA and CSA are both characterized by recurrent oscillations in tidal volume, arterial oxygen and carbon dioxide tension, sleep state, clustered bursts of sympathetic outflow, and impaired vagal heart rate modulation.[59,64] Repeated exposure to hypoxia can stimulate the production of reactive oxygen species and activate mediators of vascular inflammation.[58,65] In addition, OSA is characterized by the repetitive generation of negative intrathoracic pressure and LV afterload[59,66] at the time when myocardial metabolic gene expression and metabolic efficiency are at their nadir.[67]

In a prospective community-based population of 4022 adults followed for a median of 8.7 years, the presence of OSA was associated with an increased risk of incident HF in men but not in women.[68] Relative to HF patients without sleep apnea, the life expectancy of those with either OSA or CSA is foreshortened.[69-72]

When should it be suspected?

Because most HF patients with OSA or CSA do not complain of daytime sleepiness[73-75] or other features of sleep apnea,[59] their presence may not be considered unless a sleeping partner is also interviewed.

In a recent prospective study in 164 systolic HF patients referred for formal polysomnography, an AHI ≥ 15 events/h was detected in the majority, divided equally between OSA and CSA.[71] Of note, at a single time point, individual patients can be characterized as having predominantly (ie, > 75%) OSA or CSA,[73,76] but this proportion may change if systolic function worsens or if sleep apnea is treated.[77,78] Advances in HF therapy such as β-adrenoceptor blockade and CRT have little impact on the prevalence of either OSA or CSA.[71,73,79,80]

In men with HF, clues to the presence of OSA are obesity and drug-resistant hypertension.[73,81] The likelihood of OSA is increased further if these characteristics are present in men with dilated nonischemic cardiomyopathy, consumers of ethanol, or nocturnal blood pressure "nondippers" who are identified, for example, through ambulatory monitoring.[82] Women with OSA are often thin and elderly and present with otherwise unexplained pulmonary hypertension and tricuspid regurgitation. Following myocardial infarction, the index of suspicion should be high if there is progressive ventricular dilation despite optimal medical therapy.[83] In HF, a relative increase in septal to posterior wall hypertrophy[84] and impaired diastolic function can be additional clues to the presence of OSA.[85,86]

CSA tends to be a sign of more severe HF.[87] Its likelihood is highest in elderly hypocapnic men with atrial fibrillation or pacemakers.[73,88] Interestingly, women with systolic dysfunction rarely develop CSA.[73,76,89]

In a series of 244 consecutive HF patients with preserved LVEF, an AHI > 5 events/h was identified in 69%, with 40% classified as having OSA and 29% as having CSA. An AHI ≥ 15 events/h was present in 48%, with 25% categorized as having OSA and 23% as having CSA. Sleep apnea was associated with greater impairment of diastolic function. Similar to individuals with impaired systolic function, those with CSA had a higher average left atrial diameter, LV end-diastolic pressure, pulmonary artery and capillary wedge pressures, and plasma NT-pro-BNP concentrations.[90]

How is it diagnosed?

The diagnosis of sleep apnea is established with overnight polysomnography performed in a sleep laboratory. Current standards require the concurrent monitoring of sleep structure, cardiac rhythm, oxyhemoglobin saturation, and breathing, using noninvasive methods capable of discriminating between OSA and CSA, such as respiratory inductance plethysmography.[91,92] It is not generally appreciated that in HF, OSA often develops a periodicity resembling Cheyne-Stokes respiration.[93] It is important to establish the correct diagnosis, because there is concern that in some pa-

tients, treating CSA with continuous positive airway pressure (CPAP) may increase risk.[76,94]

How is it treated?

OSA. Nasal CPAP abolishes OSA, restoring almost immediately the normal fall in blood pressure during sleep.[59,82] Surrogate CVD endpoints have been evaluated in small short-term trials in which patients with OSA receiving contemporary HF therapy were allocated randomly to CPAP treatment. In the first of these, 1 month of CPAP reduced significantly the frequency of OSA, daytime sympathetic vasoconstrictor tone, systolic blood pressure, heart rate, and LV end-systolic dimension and increased LVEF.[74,95] Extension of this trial demonstrated, only in CPAP-treated patients, a reduction in both urinary norepinephrine excretion and ventricular ectopy during sleep[96] and during wakefulness an increase in heart rate variability[97] and its arterial baroreflex modulation.[98]

Several such observations were replicated independently by Mansfield et al.,[99] and via questionnaire, HF quality of life and functional indices also improved. A third trial comparing autotitration of positive airway pressure against subtherapeutic CPAP reported no effect on LVEF,[100] but the impact of either intervention on the AHI was not determined. CPAP may also improve myocardial metabolic efficiency.[101] It is unknown whether such short-term changes have a beneficial impact on survival.

CSA. Although pharyngeal occlusion does not initiate CSA, CPAP can attenuate CSA and Cheyne-Stokes respiration. However, reductions in the frequency of CSA tend to be gradual, require careful uptitration of applied pressure over days to weeks and are often incomplete.[64,76]

In small 3-month randomized controlled trials, attenuation of CSA was accompanied by a 30% relative increase in LVEF, reductions in nocturnal urinary norepinephrine excretion to those of matched HF patients without apnea, daytime plasma norepinephrine concentration, and mitral regurgitant fraction and improved QOL.[70,101-104]

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial was a multicentre test of the hypothesis that long-term treatment of CSA with CPAP in addition to optimal contemporary medical therapy for HF increases transplantation-free survival.[76] This trial was terminated prematurely, after 258 patients were randomized, due to a lower-than-anticipated event rate. Transplantation-free survival curves by the trial's end were identical in the 2 arms. However, patients with suppression of AHI $<$ 15 events/h had increases in LVEF and heart transplantation-free survival that were significantly greater ($P = 0.001$ and $P = 0.043$, respectively) than control.[105]

Adaptive servoventilation (ASV) has been engineered as a new method of enhancing the efficacy of positive airway pressure in CSA by sensing and responding appropriately to changes in breathing pattern. ASV has been shown to suppress CSA in patients refractory to CPAP and is as effective as CPAP for treating OSA.[106] In a recent study involving 31 HF patients with OSA or CSA, flow-triggered ASV was more effective than CPAP in reducing the AHI and had a greater positive impact, after 3 months, on LVEF.[107]

Alternatives to positive airway pressure

Short-term studies involving mandibular advancement devices to alleviate OSA have documented only modest effects on diastolic blood pressure.[108,109] Hyperoxia impairs acutely ventricular relaxation and elevates filling pressure in individuals with and without HF;[110] in short-term trials, supplemental oxygen has not been shown to improve the LVEF or quality of life of patients with CSA.[111] In single-night studies, carbon dioxide inhalation reduced CSA.[112] Atrial overdrive pacing strategies have yet to realize their initial promise;[65,113-115] the impact of CRT on sleep-related breathing disorders has not been tested as a primary outcome variable in randomized controlled trials.[65]

When should patients be referred?

There are several reasons why few HF programs routinely investigate and manage coexisting sleep apnea: its diagnosis and treatment in general fall outside the expertise and training of cardiologists, patients rarely complain of excessive daytime sleepiness, and there are no clinical trial data as yet demonstrating improved survival and less CVD morbidity with specific treatment. In those HF patients with documented OSA and daytime hypersomnolence, there is a clinical indication for referral for sleep apnea treatment. It is less clear that HF patients with CSA or OSA, without clinical indication for treatment, will benefit from sleep apnea treatment.

RECOMMENDATION

We recommend that physicians treating patients with HF encourage greater involvement in their programs of experienced sleep physicians and sleep laboratories with demonstrated capacity to discriminate between OSA and CSA using contemporary diagnostic standards (Weak Recommendation, Moderate-Quality Evidence).

We recommend CPAP for symptom relief for HF patients with OSA either who are limited by daytime hypersomnolence (Strong Recommendation, Moderate-Quality Evidence) or whose OSA initiates arrhythmias including atrial fibrillation (Weak Recommendation, Moderate-Quality Evidence).

We recommend that treatment of CSA by CPAP be considered only by personnel at centres experienced with CSA evaluation and suppression (Strong Recommendation, High-Quality Evidence).

Practical tip. Because the prevalence of coexisting OSA and CSA in patients managed by HF programs remains >50% despite contemporary medical and device therapy and because most HF patients with sleep apnea do not complain of daytime sleepiness, their evaluation should include inquiry from sleep partners into witnessed apneas, airway obstruction, and oscillating breathing patterns during sleep.

Consider OSA in HF patients presenting with paroxysmal or recurrent atrial fibrillation, hypertension refractory to optimal HF therapy, high body mass index (BMI), and unanticipated pulmonary hypertension or right ventricular (RV) dysfunction.

Consider the coexistence of sleep-related breathing disorders in HF patients when malignant ventricular arrhythmias are detected, particularly at night.

When a Patient Advances to the Terminal Stages of HF, Palliative Care Assumes an Active and Important Role

What is palliative care, and why should palliative care be used for HF patients?

Palliative care is defined as the promotion of physical and psychosocial health, regardless of diagnosis or prognosis.[116] There is growing consensus that the need for optimal palliative care extends to persons suffering from chronic, advanced noncancerous conditions such as HF.[117] HF patients often suffer from a substantial burden of noncardiac problems that go unaddressed[118-122] (Supplemental Table S2).

The majority of palliative care recipients in Canada have cancer and barriers to provision of palliative care in HF are outlined elsewhere.[117] One important barrier is the prognostic uncertainty and variable illness trajectory of HF[123]; although there are tools that may provide some prognostic guidance (Supplemental Table S3), predicting mortality in an individual HF patient remains difficult.[124-131]

Accordingly, the CCS recommendations on HF have adopted a definition for palliative care (Table 5) that is based on the World Health Organization (WHO) definition but is modified to reflect the realities of HF management.[132,133]

How should discussions about end-of-life planning and palliative care be conducted?

The goal of advance care planning (ACP) (Table 6) is to ensure that if a patient with a serious illness can no longer communicate treatment preferences, there is sufficient information available to provide care consistent with the patient's goals and values. While the objective is clearly desirable, the process can be difficult:[134] (1) generic statements are too vague to guide decisions; (2) with illness progression, patients can adapt to a state of health they previously feared, thus reconsidering treatments previously considered undesirable; and (3) unprepared surrogate decision-makers may rely on their own wishes at a time of crisis or feel compelled to honour prior commitments despite the inordinately high caregiver burden that results.

Table 5. Definition of palliative care

Palliative care is a patient-centred and family-centred approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. It is applicable early, as well as later, in the course of illness, in conjunction with other therapies that are intended to prolong life, including but not limited to in the setting of heart failure, oral pharmacotherapy, surgery, implantable device therapy, hemofiltration or dialysis, the use of intravenous inotropic agents, and ventricular assist devices.

Adapted from the WHO definition for palliative care, http://www.who.int/cancer/palliative/definition/en

Table 6. Advance care planning definition

Advance care planning (ACP) is a process whereby a patient, in conversation and reflection with family members, important others, and health care providers, makes decisions about future health care. ACP is a process of reflection on and communication of a person's goals, values, and preferences for future health care, to be used should they become incapable of giving informed consent. ACP can encompass rich conversations, which go beyond "to resuscitate or not to resuscitate" and may include meanings and fears around illness and dying, preferences for after death rituals, and spirituality.

ACP discussions involving a surrogate decision-maker[135,136] are ongoing and should foster a sense of the patient remaining in control.[135] Most patients wish to be involved in ACP, preferably when they are still relatively well.[137-139] While many clinicians are concerned that a hospitalization for an acute HF episode may not be an appropriate time for discussion, patients are more inclined to consider their future when acutely ill and thus are most receptive to discussion at those times.[140,141] Most patients are generally comfortable discussing end-of-life issues, as long as information is presented honestly and balanced with hope.[137,139,142,143] The process should involve a surrogate decision-maker early, particularly regarding leeway should a patient's previously expressed treatment wishes place an undue burden or risk on them or the decision-maker.[134,142]

How should I talk to my patient about end-of-life planning?

The first step in the proposed framework is to assess patient readiness to participate in such discussions.[134] Supplemental Table S4 provides examples of "opening lines" that could be used in assessing patient readiness.

Once patients engage in the process of end-of-life planning, the framework outlines the conduct of subsequent discussions[134] (Supplemental Table S5). The longitudinal relationship with a trusted clinician, preferably with training in effective communication skills, may facilitate such conversations.[144-147]

How should the needs of HF patients be assessed?

Potentially reversible suffering can occur in HF patients with years to live, and conversely, not all death is associated with complex suffering.[120,121,140] Palliative care interventions should be provided in response to patient needs and not be limited to individuals considered to be at end-of-life. Generic and HF-specific tools have been developed to assess the patient needs.[148-158] A meta-analysis evaluating 5 HF-specific quality of life questionnaires suggests there was no compelling evidence to recommend one tool over another.[159] Supplemental Table S6 provides a summary of HF disease-specific tools and generic/cancer tools that may be applicable in HF patients and for caregiver needs.[160]

How should the symptoms associated with HF be managed?

It is important to ensure that all potential HF-specific therapies have been considered for patients with advanced HF.[1] Discontinuation of unnecessary medications should be considered.[161] In addition, insertion of devices, use of inotropic infusions, and dialysis should only proceed after

exploring the circumstances in which the patient might want these discontinued, as well as other alternatives such as comfort-focused care.

Generic symptom relief strategies may be applied concurrently with HF management (Supplemental Table S6). The evidence base for these strategies is primarily derived from cancer care. Opioids may be preferred over benzodiazepines for dyspnea.[162,163] Functional impairment is common at the end-of-life and a significant source of distress.[164] All patients with NYHA I to III HF should be referred to cardiac rehabilitation.[1] Emerging evidence suggests that tailored exercise programs may lead to improvements in quality of life even among HF patients nearing the end of life.[164]

Supplemental Table S7 reflects common Canadian palliative care practice.[165] Cardiac-specific palliative treatment algorithms have been developed but not validated.[166,167] The use of end-of-life care pathways may improve the quality of care for dying patients.[168]

How should the care of patients with HF be organized?

The Canadian Heart Health Strategy and Action Plan outlines a strategy to reduce the growing burden of CVD in Canada and has endorsed the chronic care model (CCM) as the optimal framework to ensure timely access to cardiac rehabilitation and end-of-life care.[169-171] Within the CCM, care is patient-centred and builds on six evidence-based core elements designed to work together to improve health outcomes[172] (Supplemental Table S8).

Promoting self-care is a key component of CDM.[173] In advanced HF, self-care activities may include maintaining a safe home environment or implementing measures for treating distressing symptoms at home rather than in the hospital.[174] Evidence supporting the CCM comes from a randomized controlled trial of an in-home palliative care program for older patients, 33% with HF.[175] The intervention was based on self-management support provided by an interdisciplinary team including a physician, nurse, and social worker providing home-based assessment and ongoing care planning, delivery, and coordination. The intervention resulted in a significant decrease in emergency department visits, hospitalizations, and in-hospital deaths.

RECOMMENDATION

We recommend that clinicians looking after HF patients should initiate and facilitate regular discussions with patients and family regarding advance care planning (Strong Recommendation, Low-Quality Evidence).

Practical tip. The timing of discussions should strongly consider the high mortality rate in the year following a first HF hospitalization.

A surrogate decision-maker should be identified early and regularly participate in these discussions.

RECOMMENDATION

We recommend that the provision of palliative care to patients with HF should be based on a thorough assessment of needs and symptoms, rather than on individual estimate of remaining life expectancy (Strong Recommendation, Low-Quality ofEvidence).

We recommend that the presence of persistent advanced HF symptoms (NYHA III-IV) despite optimal therapy be confirmed, ideally by an interdisciplinary team with expertise in HF management, to ensure appropriate HF management strategies have been considered and optimized, in the context of patient goals and comorbidities (Strong Recommendation, Low-Quality Evidence).

We recommend an interdisciplinary CCM for the organization and delivery of palliative care to patients with advanced HF (Strong Recommendation, Low-Quality Evidence).

When the Patient Is in Severe or Terminal HF: What Can Mechanical Circulatory Support Devices Do for Them?

What is mechanical circulatory support?

Mechanical circulatory support (MCS) is a group of technologies that increase forward cardiac output in patients.[176-178] Intra-aortic balloon pump counterpulsation, although technically a form of MCS,[179] is now used only when a rapidly available therapy is needed for a very limited cardiac augmentation. MCS therapies consist of ventricular assist devices (VADs) that augment or replace the ventricle. They may be used to assist the right ventricle (RVAD), LV (LVAD), or both ventricles (BiVAD).[176] The choice depends on the clinical presentation.

What is the purpose of MCS?

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) group has published a classification for the clinical presentations of advanced HF to be used for determination of the timing for potential MCS therapy (Supplemental Table S9). In general, MCS should be considered for patients with advanced HF or rapidly progressing HF who don't respond to standard treatment.[180,181] Since such patients may suddenly and unpredictably become too ill for even MCS, referral for MCS should be made early on.[182]

MCS may be offered as either short- or long-term therapy (Supplemental Table S10)

Short-Term. These devices are generally utilized for acute clinical presentations to allow time (a few hours to a few days) to determine if transition to transplantation, a long-term device, or explantation is appropriate.[183-187] Examples include extracorporeal membrane oxygenation (ECMO),[188-192] surgically implanted pumps,[193-195] and percutaneous or surgically implanted devices.[196,197]

Long-Term. These devices are used for longer term support, are more reliable, provide better cardiac support, and are associated with fewer complications.[176,198]

First-generation VADs consisted of an inflow cannula from the ventricle to a chamber, which, when filled, would then empty into an outflow cannula affixed to the ascending aorta.[178,199-203] Second- and third-generation VADs still require percutaneous drive lines but are nonpulsatile in nature, have fewer moving parts, and demonstrate significantly improved ease of implantation, use, and follow-up as well as durability to over 5 years.[204-214] At present, only LV support is feasible for long-term support. Supplemental Table S11 indicates a general framework for insertion of an MCS.

MCS may be offered as 1 of 5 strategies

The use of MCS is indicated in 5 different situations: (1) bridge to decision is used primarily with short-term devices; (2) bridge to recovery provides support until recovery when the device is explanted; (3) bridge to transplantation (BTT) is most common and supports the patient until transplantation;[209,215-218] and (4) bridge to candidacy (BTC) are potentially eligible for transplant, and receive MCS until they become eligible. If they remain ineligible, a decision is made to terminate MCS or to continue as destination therapy (DT); (5) DT is long-term MCS for patients who are ineligible for transplant but otherwise have a good life expectancy.

Provision of MCS to patients with advanced HF improves function in nearly every major organ, provided irreversible injury has not occurred.[219] Less than 5% of patients have the device removed without transition to transplantation.[183,184,186,220-222]

Additionally, studies have shown MCS for patients with selected contraindications for transplantation may result in reversal of these conditions and transplantation is no longer contraindicated.[178,201,206,207,223-232] Studies have suggested MCS may be superior to inotrope infusion in inotrope-dependent patients awaiting transplantation and where wait times for transplantation may be very long.[230,233]

The use of DT is increasing because of unsuccessful attempts at BTC or direct DT.[208,234-239] To date, only 2 randomized studies have reported on the use of MCS in transplantation-ineligible patients.

In the multicentre Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial (REMATCH), 129 patients with end-stage HF, not eligible for cardiac transplantation, were randomized to MCS (HeartMate XVE) or medical therapy.[240,241] The 1-year survival rates were 52% in the MCS group and 25% in the medical group ($P = 0.002$); at 2 years, rates were 23% and 8% ($P = 0.09$), respectively, with improved quality of life.[231,242] Unfortunately, at 2 years, survival in the VAD group was $< 10\%$, with most mortality arising from multiple organ failure, stroke, infection, or device failure.

The continuous-flow VAD has led to a significant improvement in outcomes[204,243-245] with several devices available,[246-249] although in Canada the most common one is the HeartMate II.[197,238,250] In a randomized trial of 200 HF transplant ineligible patients the HeartMate II was compared to the HeartMate XVE.[251] The primary endpoint of freedom from disabling stroke or reoperation for repair or replacement of the device at 2 years was significantly lower in the HeartMate II group (46% vs 11%, $P < 0.001$). Cost analysis of the HeartMate XVE, compared with medical therapy, demonstrated a cost per life-year saved of US$50,000-US$100,000, which compares favourably to renal replacement therapy.[252] The estimated cost of the medical therapy group over the course of the study exceeded US$150,000, illustrating the enormous costs associated with medical treatment for end-stage HF.[253]

Most studies have excluded patients who represented very high operative risk or those with other comorbidities that adversely affect long-term outcomes.[180,181,194,221,243,244,250,254-269] Bleeding diathesis, presence of multiorgan failure, presence of multiple comorbidities, and need for RV support are highly predictive of poor outcomes. Advancing age is also a risk factor, but this is based on a small number of recipients aged > 75 years.[262,263]

Who should provide MCS therapy?

There arevirtually no data regarding short- or long-term outcomes of MCS therapy outside those with a large volume of experience in the treatment of advanced HF.[197,238,270] Analysis of the INTERMACS registry suggests that centres with annual VAD volumes of < 5 cases have worse outcomes.[182,220,222]

What are the problems associated with MCS?

In most high-volume MCS centres, early survival of MCS surgery approaches 85%-90%, depending upon patient selection. Thus, for long-term implantations, most mortality now occurs later. Complications following institution of MCS may be divided into those occurring early (the perioperative period out to 30 days) and late (any time after 30 days).

The early complications are as follows. Postoperative bleeding is the most common problem (up to 50%-60%) and is frequently implicated in early death.[178,197,204,209,248,271-277] Vascular injury can occur due to insertion either percutaneously or via surgical cutdown and increases with the duration of support.[176,244] RV failure following the institution of left-sided MCS is of particular concern, as the mortality dramatically rises.[193,194,258,260,261,267,278-280] Patients are as prone to the usual array of postoperative infections as are any other cardiac surgical patient.[281-283] The majority present in a low-flow state, which frequently compromises end-organ function. This complication is associated with $> 50\%$ mortality and is most frequently a consequence of late referral.

The late complications following MCS surgery[222,259] are as follows. Thromboembolism and bleeding, with continuous-flow devices, is seen in $<10\%$ of cases.[204,248] Bleeding complications are more common with continuous-flow devices, due to platelet dysfunction and development of arteriovenous malformations, primarily in the gut.[276,284] Hemolysis is common but usually minor.[285] Infection is a common complication.[202,259,286-290] In general, with newer devices, rates of malfunction will be $\sim$10% per year of follow-up.[251] MCS patients are prone, through a number of mechanisms, to the generation of allosensitization[226,233] leading to incompatibility or rejection of transplanted hearts.[218] The aortic valve may also fuse and develop aortic stenosis or insufficiency.[236,256,291-294] Despite these complications, reports suggest 2-year survival with MCS approaches 60%, which compares favourably to patients with moderately severe HF without MCS.[231,237]

Special Considerations in Patients With Continuous-Flow Devices

Several physiologic changes occur in the circulation that will affect the manner in which patients are examined and followed.

Measurement of systemic pressure requires a blood pressure cuff and Doppler probe, which will provide a mean blood pressure.[252] VADs are afterload dependent and thus it is important that mean blood pressure is < 90 mm Hg and preferably < 85 mm Hg.

A survey of high-volume MCS centres with an estimated combined patient-year exposure to MCS of > 200 years found there were no reported cases of a sudden loss of consciousness.[295] Thus, driving short distances may be safe and feasible for stable ambulatory patients, provided device battery charge is adequate.

RECOMMENDATION

We recommend that patients with either acute severe or chronic advanced HF and with an otherwise good life expectancy be referred to a fully equipped cardiac centre for assessment and management by a team with expertise in the treatment of severe HF, including MCS (Strong Recommendation, Moderate-Quality Evidence).

We recommend MCS be considered for patients who are listed for cardiac transplantation and who deteriorate or are otherwise not likely to survive until a suitable donor organ is found (Strong Recommendation, Moderate-Quality Evidence).

We recommend that MCS be considered for patients for whom there is a contraindication for cardiac transplantation but may, via MCS, be rendered transplant eligible (Strong Recommendation, Low-Quality Evidence).

We recommend that patients with fulminant HF be considered for temporary MCS to afford an opportunity for evaluation for long-term options (Strong Recommendation, Moderate-Quality Evidence) (Supplemental Table S10).

We recommend permanent MCS be considered for highly selected transplant ineligible patients (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the potential variability of patient preference as well as the need to interact with the patient to ensure the choice reflects the patient's values, with less value on the effectiveness of therapy.

RECOMMENDATION

We recommend that institutions providing MCS therapy develop a policy regarding DT within the conventions, resources, and philosophy of care of their organization (Weak Recommendation, Low-Quality Evidence).

We recommend that ambulatory patients with MCS therapy who are discharged from hospital and who have had minimal HF symptoms or ventricular arrhythmias for a period of at least 1 month be considered candidates for operation of a personal motor vehicle for a period not exceeding two thirds of the known battery charge time (Weak Recommendation, Low-Quality Evidence).

Practical tip

Candidacy for MCS. Candidates are patients with advanced HF, including those, despite optimal treatment, continuing to exhibit NYHA IIIb or IV HF symptoms AND accompanied by MORE THAN ONE OF the following:

- LVEF < 25% and, if measured, peak exercise oxygen consumption <14 mL/kg/min
- Evidence of progressive end organ dysfunction due to reduced perfusion not due to inadequate ventricular filling pressures
- Recurrent HF hospitalizations (> 3 in 1 year) not due to a clearly reversible cause
- Need to progressively reduce or eliminate evidence-based HF therapies such as ACE inhibitors or β-blockers, due to symptomatic hypotension or worsening renal function
- Requirement for inotropic support

MCS-performing centres. Cardiac centres that perform MCS should have adequate manpower and resources for support of patients requiring MCS support. These include:

- An identified and adequately trained multidisciplinary MCS team
- Access to the full array of medical and surgical consultative support, and institutional administrative and financial support
- Expertise in MCS implantation, follow-up, and explantation

Conclusions

Recent studies have confirmed the use of CRT and aldosterone receptor blockade even in patients with less symptomatic HF. The importance of heart rate lowering has been highlighted, and an agent such as ivabradine, once marketed in Canada, may have the potential to further reduce morbidity in patients with persistently elevated heart rates. Sleep apnea should be considered in HF patients and, when indicated, assessment should be undertaken in a qualified sleep laboratory. The field of palliative care is reviewed. Once emphasized only in cancer, palliative care plays an important role in the management of patients with advanced HF. Finally, the rapidly expanding field of MCS is reviewed with respect to the current indications for treatment.

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References

1. Arnold JMO, Liu P, Demers C, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 2006;22:23-45.

2. Arnold JMO, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol 2007;23:21-45.

3. Arnold JMO, Howlett JG, Ducharme A, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure-2008 update: Best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. Can J Cardiol 2008;24:21-40.

4. Howlett JG, McKelvie RS, Arnold JMO, et al. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. Can J Cardiol 2009;25:85-105.

5. Howlett JG, McKelvie RS, Costigan J, et al. The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: heart failure in ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs. Can J Cardiol 2010;26:185-202.

6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336: 924-926.

7. St John Sutton MG, Abraham WT, Smith AL, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985-90.

8. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol 2003;42: 1454-9.

9. Abraham WT, Young JB, León AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation 2004;110:2864-8.

10. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.

11. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.

12. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.

13. Al-Majed NS, McAlister FA, Bakal JA, et al. Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. Ann Intern Med 2011;154:401-12.

14. Funder JW. Reconsidering the roles of the mineralocorticoid receptor. Hypertension 2009;53:286-290.

15. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J 2009;30:469-77.

16. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.

17. Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomized controlled trial. Lancet 2008;372:817-21.

18. Diaz A, Bourassa MG, Guertin MC, et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967-74.

19. Flannery G, Gehrig-Mills R, Billah B, et al. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol 2008;101:865-9.

20. McAlister FA, Wiebe N, Ezekowitz JA, et al. Meta-analysis: β-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 2009;150:784-94.

21. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe, Part 2: treatment. Eur Heart J 2003;24:464-74.

22. Komajda M, Hanon O, Hochadel M, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. Eur Heart J 2009;30:478-86.

23. Savelieva I, Camm AJ. I_f inhibition with ivabradine electrophysiological effects and safety. Drug Saf 2008;31:95-107.

24. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. Lancet 2010; 376:875-85.

25. Fox K, Ford I, Steg G, et al; on behalf of the BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL Trial. Eur Heart J 2009;30:2337-45.

26. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383-92.

27. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro b-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-pro-BNP Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. J Am Coll Cardiol 2010;55:53-60.

28. Eurlings LWM, van Pol PEJ, Kok WE, et al. Management of chronic heart failure guided by individual N-terminal pro B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) Study. J Am Coll Cardiol 2010;56:2090-100.

29. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. Circulation 2010;121:2592-600.

30. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010;31:703-11.

31. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-96.

32. Damman K, van Deursen VM, Navis G, et al. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009;53:582-8.

33. Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006; 47:1987-96.

34. Harnett JD, Foley RN, Kent GM, et al. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int 1995;47: 884-90.

35. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

36. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39:S1-246.

37. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the

Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.

38. Palevsky PM. Renal replacement therapy I: indications and timing. Crit Care Clin 2005;21:347-56.

39. Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol 2003;41:1438-44.

40. Winkelmayer WC, Charytan DM, Levin R, et al. Poor short-term survival and low use of cardiovascular medications in elderly dialysis patients after acute myocardial infarction. Am J Kidney Dis 2006;47:301-8.

41. Zannad F, Kessler M, Lehert P, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int 2006;70:1318-24.

42. Suzuki H, Kanno Y, Sugahara S, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis 2008;52:501-6.

43. Cice G, Di BA, D'Isa S, et al. Effects of telmisartan added to Angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. J Am Coll Cardiol 2010;56:1701-8.

44. Hussain S, Dreyfus DE, Marcus RJ, et al. Is spironolactone safe for dialysis patients? Nephrol Dialysis Transpl 2003;18:2364-8.

45. Saudan P, Mach F, Perneger T, et al. Safety of low-dose spironolactone administration in chronic haemodialysis patients. Nephrol Dialysis Transpl 2003;18: 2359-63.

46. Evan G, Marcos R, Susan D, et al. Effect of spironolactone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric hemodialysis patients [abstract]. Am J Kidney Dis 2005;46:94-101.

47. Taheri S, Mortazavi M, Shahidi S, et al. Spironolactone in chronic hemodialysis patients improves cardiac function. Saudi J Kidney Dis Transpl 2009;20:392-7.

48. Knoll G, Cockfield S, Blydt-Hansen T, et al. Canadian Society of Transplantation: consensus guidelines on eligibility for kidney transplantation. CMAJ 2005; 173:S1-25.

49. Ferreira SR, Moises VA, Tavares A, et al. Cardiovascular effects of successful renal transplantation: a 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. Transplantation 2002;74: 1580-7.

50. Wali RK, Wang GS, Gottlieb SS, et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. J Am Coll Cardiol 2005;45: 1051-60.

51. Parfrey PS, Harnett JD, Foley RN, et al. Impact of renal transplantation on uremic cardiomyopathy. Transplantation 1995;60:908-14.

52. Fonarow GC, Corday E. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev 2004;9: 179-85.

53. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97:1759-64.

54. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004;147:331-8.

55. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol 2005;46:2043-6.

56. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-83.

57. Kazory A, Ross EA. Contemporary trends in the pharmacological and extracorporeal management of heart failure: a nephrologic perspective. Circulation 2008; 117:975-83.

58. Bradley TD, Floras JF. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009;373:82-93.

59. Bradley TD, Floras JS. Sleep apnea and heart failure: part I: obstructive sleep apnea. Circulation 2003;107:1671-8.

60. Shiota JS, Ryan CM, Chiu KL, et al. Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. Thorax 2007;62:868-72.

61. Yumino D, Redolfi S, Ruttanaumpawan P, et al. Nocturnal rostral fluid shift: a unifying concept for the pathogenesis of obstructive and central sleep apnea in men with heart failure. Circulation 2010;1598-605.

62. Giannoni A, Emdin M, Poletti R, et al. Clinical significance of chemosensitivity in chronic heart failure: influence on neurohormonal derangement, Cheyne-Stokes respiration and arrhythmias. Clin Sci 2008;114:489-97.

63. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol 2009;54:375-85.

64. Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. Circulation 2003;107:1822-6.

65. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Circulation 2008;118:1080-111.

66. Floras JS, Bradley TD. Treating obstructive sleep apnea: is there more to the story than 2 millimeters of mercury? Hypertension 2007;50:289-91.

67. Young ME. The circadian clock within the heart: potential influence on myocardial gene expression, metabolism, and function. Am J Physiol Heart Circ Physiol 2006;290:H1-H16.

68. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. Circulation 2010;352-60.

69. Lanfranchi PA, Braghiroli A, Bosimini E, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation 1999;99:1435-40.

70. Sin DD, Logan AG, Fitzgerald FS, et al. Effects of continuous positive airway pressure on long-term outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 2000;102:61-6.

71. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol 2007;49:1625-31.

72. Javaheri S, Shukla R, Zeigler H, et al. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007;49:2028-34.

73. Sin D, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101-6.

74. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233-41.

75. Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. Arch Intern Med 2006;166:1716-22.

76. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025-33.

77. Tkacova R, Niroumand M, Lorenzi-Filho G, et al. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO2 and circulatory delay. Circulation 2001;103:238-43.

78. Ryan CM, Floras JS, Logan AG, et al. Shift in sleep apnea type in heart failure patients in the CANPAP Trial. Eur Respir J 2010;592-7.

79. MacDonald M, Fang J, Pittman SD, et al. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta-blockers. Clin Sleep Med 2008;4:38-42.

80. Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J 2011;32:61-74.

81. Sin DD, Fitzgerald F, Parker JD, et al. Relationship of systolic BP to obstructive sleep apnea in patients with heart failure. Chest 2003;123:1536-43.

82. Tkacova R, Rankin F, Fitzgerald FS, et al. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation 1998;98:2269-75.

83. Nakashima H, Katayama T, Takagi C, et al. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. Eur Heart J 2006;27:2317-22.

84. Usui K, Parker JD, Newton GE, et al. Left ventricular structural adaptations to obstructive sleep apnea in dilated cardiomyopathy. Am J Respir Crit Care Med 2006;173:1170-5.

85. Arias MA, Garcia-Rio F, Alonso-Fernandez A, et al. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation 2005;112:375-83.

86. Kim SH, Cho GY, Shin C, et al. Impact of obstructive sleep apnea on left ventricular diastolic function. Am J Cardiol 2008;101:1663-8.

87. Oldenburg O, Lamp B, Faber L, et al. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;251-7.

88. Oldenberg O, Bitter T, Wiemer M, et al. Pulmonary capillary wedge pressure and pulmonary arterial pressure in heart failure patients with sleep-disordered breathing. Sleep Med 2009;10:726-30.

89. O'Meara E, Clayton T, McEntegart MB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007;115:3111-20.

90. Bitter T, Faber L, Hering D, et al. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail 2009;11:602-8.

91. The report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-89.

92. Redline S, Budhiraja R, Kapur V, et al. The scoring of respiratory events in sleep: reliability and validity. J Clin Sleep Med 2007;3:169-200.

93. Ryan CM, Bradley TD. Periodicity of obstructive sleep apnea in patients with and without heart failure. Chest 2005;127:536-42.

94. Floras JS. Should sleep apnoea be a specific target of therapy in chronic heart failure? Heart 2009;95:1041-6.

95. Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Card 2005;45:2008-11.

96. Ryan CM, Usui K, Floras JS, et al. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax 2005;60:781-5.

97. Gilman MP, Floras JS, Usui K, et al. Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea. Clin Sci 2008;114:243-9.

98. Ruttanaumpawan P, Gilman MP, Usui K, et al. Sustained effect of continuous positive airway pressure on baroreflex sensitivity in congestive heart failure patients with obstructive sleep apnea. J Hypertens 2008;26:1163-8.

99. Mansfield D, Gollogly NC, Kaye DM, et al. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med 2004;169:361-6.

100. Smith LA, Vennelle M, Gardner RS, et al. Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. Eur Heart J 2007;28: 1221-7.

101. Yoshinaga K, Burwash IG, Leech JA, et al. The effects of continuous positive airway pressure on myocardial energetics in patients with heart failure and obstructive sleep apnea. J Am Coll Cardiol 2007;49:450-8.

102. Naughton MT, Liu PP, Bernard DC, et al. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 1995;151:92-7.

103. Tkacova R, Liu PP, Naughton MT, et al. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. J Am Coll Cardiol 1997;30:739-45.

104. Naughton MT, Benard DC, Liu PP, et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995;152:473-9.

105. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007;115: 3173-80.

106. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest 2008; 134:61-6.

107. Kasai T, Usui Y, Yoshioka T, et al. Effect of flow-triggered adaptive servoventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. Circ Heart Fail 2010;3:140-8.

108. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. Sleep 2004; 27:934-41.

109. Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:656-64.

110. Mak S, Azevedo E, Liu P, et al. Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. Chest 2001;120:467-73.

111. Staniforth AD, Kinnear WJM, Starling R, et al. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J 1998;19:922-8.

112. Szollosi I, Jones M, Morrell MJ, et al. Effect of CO2 inhalation on central sleep apnea and arousals from sleep. Respiration 2004;71:493-8.

113. Pepin JL, Defaye P, Garrigue S, et al. Overdrive atrial pacing does not improve obstructive sleep apnea syndrome. Eur Respir J 2005;25:343-7.

114. Floras JS, Bradley TD. Atrial overdrive pacing for sleep apnea; a door now closed? Am J Respir Crit Care Med 2005;172:118-22.

115. Manistry CH, Willson K, Davies JE, et al. Induction of oscillatory ventilation pattern using dynamic modulation of heart rate through a pacemaker. Am J Physiol 2008;295:R219-27.

116. Coventry PA, Grande GE, Richards DA, et al. Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: a systematic review. Age Ageing 2005;34:218-27.

117. Howlett J, Morin L, Fortin M, et al. End-of-life planning in heart failure: it should be the end of the beginning. Can J Cardiol 2010;26:135-41.

118. Anderson H, Ward C, Eardley A, et al. The concerns of patients under palliative care and a heart failure clinic are not being met. Palliat Med 2001;15:279-86.

119. Boyd KJ, Murray SA, Kendall M, et al. Living with advanced heart failure: a prospective, community based study of patients and their carers. Eur J Heart Fail 2004;6:585-91.

120. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symp Manage 2006;31:58-69.

121. O'Leary N, Murphy NF, O'Loughlin C, et al. A comparative study of the palliative care needs of heart failure and cancer patients. Eur J Heart Fail 2009; 11:406-12.

122. 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;2:213-7.

123. Gott M, Barnes S, Parker C, et al. Dying trajectories in heart failure. Palliat Med 2007;21:95-9.

124. Lee DS, Austin PC, Rouleau JL, et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581-7.

125. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424-33.

126. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660-7.

127. Moss AH, Lunney JR, Culp S, et al. Prognostic significance of the "surprise" question in cancer patients. J Palliat Med 2010;13:837-40.

128. Moss AH, Ganjoo J, Sharma S, et al. Utility of the "surprise" question to identify dialysis patients with high mortality. Clin J Am Soc Nephrol 2008;3:1379-84.

129. Head B, Ritchie CS, Smoot TM. Prognostication in hospice care: can the palliative performance scale help? J Palliat Med 2005;8:492-502.

130. Harrold J, Rickerson E, Carroll JT, et al. Is the palliative performance scale a useful predictor of mortality in a heterogeneous hospice population? J Palliat Med 2005;8:503-9.

131. Brezinski D, Stone PH, Muller JE, et al. Prognostic significance of the Karnofsky Performance Status score in patients with acute myocardial infarction: comparison with the left ventricular ejection fraction and the exercise treadmill test performance. The MILIS Study Group. Am Heart J 1991;121:1374-81.

132. Hupcey JE, Penrod J, Fenstermacher K. A model of palliative care for heart failure. Am J Hosp Palliat Care 2009;26:399-404.

133. Thompson KA, Bharadwaj P, Philip KJ, et al. Heart failure therapy: beyond the guidelines. J Cardiovasc Med 2010;11:919-27.

134. Sudore RL, Fried TR. Redefining the "planning" in advance care planning: preparing for end-of-life decision making. Ann Intern Med 2010 17;153:256-61.

135. Davidson PM. Difficult conversations and chronic heart failure: do you talk the talk or walk the walk? Curr Opin Support Palliat Care 2007;1: 274-8.

136. Harding R, Selman L, Beynon T, et al. Meeting the communication and information needs of chronic heart failure patients. J Pain Symptom Manage 2008;36:149-56.

137. Heyland DK. Tranmer J, Feldman-Stewart D. End-of-life decision making in the seriously ill hospitalized patient: an organizing framework and results of a preliminary study. J Palliat Care 2000;16:S31-9.

138. Laakkonen M-L, Pitkala KH, Strandberg TE, et al. Older people's reasoning for resuscitation preferences and their role in the decision-making process. Resuscitation 2005;65:165-71.

139. Caldwell PH, Arthur HM, Demers C. Preferences of patients with heart failure for prognosis communication. Can J Cardiol 2007;23:791-6.

140. Formiga F, Chivite D, Ortega C, et al. End-of-life preferences in elderly patients admitted for heart failure. QJM 2004;97:803-8.

141. Hauptman PJ, Havranek EP. Integrating palliative care into heart failure care. Arch Intern Med 2005;165:374-8.

142. Frank C, Heyland DK, Chen B, et al. Determining resuscitation preferences of elderly inpatients: a review of the literature. CMAJ 2003;169: 795-9.

143. Heyland DK, Dodek P, Rocker G, et al. Canadian Researchers End-of-Life Network (CARENET). What matters most in end-of-life care: perceptions of seriously ill patients and their family members. CMAJ 2006; 174:627-33.

144. Buckman R. Communication skills in palliative care: a practical guide. Neurol Clin 2001;19:989-1004.

145. Clayton JM, Hancock KM, Butow PN, et al. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. Med J Aust 2007;186:S77-108.

146. Buckman R. Words that make a difference: enhancing the "How" in "How we say it." Support Cancer Ther 2006;3:127.

147. Pantilat SZ. Communicating with seriously ill patients: better words to say. JAMA 2009;301:1279-81.

148. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J 1992;124:1017-25.

149. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.

150. Wiklund I, Lindvall K, Swedberg K, et al. Self-assessment of quality of life in severe heart failure. Scand J Psychol 1987;28:220-5.

151. Guyatt GH, Nogradi S, Halcrow S, et al. Development and testing of a new measure of health status for clinical trials in heart failure. Gen Intern Med 1989;4:101-7.

152. O'Leary CJ, Jones PW. The left ventricular dysfunction questionnaire (LVD-36): reliability, validity, and responsiveness. Heart 2000; 83:634-40.

153. Zambroski CH, Lennie T, Chung ML, et al. Use of the Memorial Symptom Assessment Scale—Heart Failure in heart failure patients. Circulation 2004;110(suppl III):17.

154. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method of the assessment of palliative care patients. Journal of Palliative Care 1991;7:69.

155. Garratt A, Schmidt L, Mackintosh A, et al. Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 2002;324:1417.

156. Fadol A, Mendoza T, Gning I, et al. Psychometric testing of the MDASI-HF: a symptom assessment instrument for patients with cancer and concurrent heart failure. J Card Fail 2008;14:497-507.

157. Glajchen M, Kornblith A, Homel P, et al. Development of a brief assessment scale for caregivers of the medically ill. J Pain Symptom Manage 2005;29:245-54.

158. Heyland DK, Cook DJ, Rocker GM, et al. Canadian Researchers at the End of Life Network. The development and validation of a novel questionnaire to measure patient and family satisfaction with end-of-life care: the Canadian Health Care Evaluation Project (CANHELP) Questionnaire. Palliat Med 2010;24:682-95.

159. Garin O, Ferrer M, Pont A, et al. Disease-specific health-related quality of life questionnaires for heart failure: a systematic review with meta-analyses. Qual Life Res 2009;18:71-85.

160. Hudson PL, Trauer T, Graham S, et al. A systematic review of instruments related to family caregivers of palliative care patients Pall Med 2010;24:656-68.

161. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium." JAMA 2010;304:1592-601.

162. Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. Thorax 2002;57:939-44.

163. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev 2010;:CD007354.

164. Eva G, Wee B. Rehabilitation in end-of-life management. Curr Opin Support Palliat Care 2010;4:158-62.

165. JL Pereira Associates. Pallium Palliative Pocketbook: A Peer-Reviewed, Referenced Resource. Edmonton, Canada: The Pallium Project, 2008.

166. SW London Cardiac Network. Available at: http://www.slcsn.nhs.uk/files/cardiac/swl-symptom-control-guidelines.pdf. Accessed on March 3, 2011.

167. National End of Life Care Programme. End of life care in heart failure: a framework for implementation. Available at: http://www.improvement.nhs.uk/LinkClick.aspx?fileticket=KBUUEsR0mms%3d&tabid=56. Accessed on March 3, 2011.

168. Walker R, Read S. The Liverpool Care Pathway in intensive care: an exploratory study of doctor and nurse perceptions. Int J Palliat Nurs 2010;16:267-73.

169. Arthur HM, Suskin N, Bayley M, et al. The Canadian Heart Health Strategy and Action Plan: cardiac rehabilitation as an exemplar of chronic disease management. Can J Cardiol 2010;26:37-41.

170. Wagner EH, Austin BT, Davis C, et al. Improving Chronic illness Care: Translating Evidence Into Action. Health Affairs 2001;20:64-78.

171. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA 2002;288:1775-9.

172. Coleman K, Austin BT, Brach C, et al. Evidence on the chronic care model in the new millennium. Health Affairs 2009; 28:75-85.

173. Hopp FP, Thornton N, Martin L. The lived experience of heart failure at the end of life: a systematic literature review. Health Soc Work 2010;25:109-17.

174. Riegel B, Moser DK, Anker SD, et al. State of the Scinece. Promoting self-care in persons with heart failure. A scientific statement from the American Heart Association. Circulation 2009;120:1141-63.

175. Brumley R, Enguidanos S, Jamison P, et al. Increased satisfaction with care and lower costs: results of a randomized trial of in-home palliative care. JAGS 2010;55:993-1000.

176. Boehmer JP, Popjes E. Cardiac failure: mechanical support strategies. Crit Care Med 2006;34(9 suppl):S268-77.

177. Chu SH, Hsu RB. Current status of artificial hearts and ventricular assist devices. J Formos Med Assoc 2000;99:79-85.

178. Kanter KR, McBride LR, Pennington DG, et al. Bridging to cardiac transplantation with pulsatile ventricular assist devices. Ann Thorac Surg 1988;46:134-40.

179. Goldman BS, Walker P, Gunstensen J, et al. Intra-aortic balloon pump assist: adjunct to surgery for left ventricular dysfunction. Can J Surg 1976;19:128-34.

180. Aaronson KD, Patel H, Pagani FD. Patient selection for left ventricular assist device therapy. Ann Thorac Surg 2003;75(6 suppl):S29-35.

181. Mielniczuk L, Mussivand T, Davies R, et al. Patient selection for left ventricular assist devices. Artif Organs 2004;28:152-7.

182. Lietz K, Long JW, Kfoury AG, et al. Impact of center volume on outcomes of left ventricular assist device implantation as destination therapy: analysis of the Thoratec HeartMate Registry, 1998 to 2005. Circ Heart Fail 2009;2:3-10.

183. Arbustini E, Grasso M, Porcu E, et al. Healing of acute myocarditis with left ventricular assist device: morphological recovery and evolution to the aspecific features of dilated cardiomyopathy. Ital Heart J 2001;2:55-9.

184. El-Hamamsy I, White M, Pellerin M, et al. Successful explantation of a left ventricular assist device following acute fulminant myocarditis. Can J Cardiol 2006;22:507-8.

185. Farrar DJ, Holman WR, McBride LR, et al. Long-term follow-up of Thoratec ventricular assist device bridge-to-recovery patients successfully removed from support after recovery of ventricular function. J Heart Lung Transplant 2002;21:516-21.

186. Delgado DH, Ross HJ, Rao V. The dilemma of a left ventricular assist device explantation: a decision analysis. Can J Cardiol 2007;23:657-61.

187. Slaughter MS, Sobieski MA, Koenig SC, et al. Left ventricular assist device weaning: hemodynamic response and relationship to stroke volume and rate reduction protocols. ASAIO J 2006;52:228-33.

188. Chung JC, Tsai PR, Chou NK, et al. Extracorporeal membrane oxygenation bridge to adult heart transplantation. Clin Transplant 2010;24:375-80.

189. Ko WJ, Lin CY, Chen RJ, et al. Extracorporeal membrane oxygenation support for adult postcardiotomy cardiogenic shock. Ann Thorac Surg 2002;73:538-45.

190. Pagani FD, Lynch W, Swaniker F, et al. Extracorporeal life support to left ventricular assist device bridge to heart transplant: a strategy to optimize survival and resource utilization. Circulation 1999;100(19 suppl):II-206-10.

191. Ibrahim M, Hendry P, Masters R, et al. Management of acute severe perioperative failure of cardiac allografts: a single-centre experience with a review of the literature. Can J Cardiol 2007;23:363-7.

192. Pagani FD, Aaronson KD, Swaniker F, et al. The use of extracorporeal life support in adult patients with primary cardiac failure as a bridge to implantable left ventricular assist device. Ann Thorac Surgr 2001;71: S77-81.

193. Chen JM, Levin HR, Catanese KA, et al. Use of a pulsatile right ventricular assist device and continuous arteriovenous hemodialysis in a 57-year-old man with a pulsatile left ventricular assist device. J Heart Lung Transplant 1995;14:186-91.

194. Morgan JA, John R, Lee BJ, et al. Is severe right ventricular failure in left ventricular assist device recipients a risk factor for unsuccessful bridging to transplant and post-transplant mortality. Ann Thorac Surg 2004;77: 859-63.

195. Samuels L, Holmes EC, Hagan K, et al. Incorporation of an in-line filter for ultrafiltration or hemodialysis to the Abiomed BVS5000 ventricular assist device. ASAIO J 2006;52:634-7.

196. Cheung A, Bashir J, Kaan A, et al. Minimally invasive, off-pump explant of a continuous-flow left ventricular assist device. J Heart Lung Transplant 2010;29:808-10.

197. El-Hamamsy I, Jacques F, Perrault LP, et al. Results following implantation of mechanical circulatory support systems: the Montreal Heart Institute experience. Can J Cardiol 2009;10710.

198. Russell SD, Miller LW, Pagani FD. Advanced heart failure: a call to action. Congest Heart Fail 2008;14:316-321.

199. Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg 1995;222:327-36.

200. Haft JW, Suzuki Y, Aaronson KD, et al. Identification of device malfunction in patients supported with the HeartMate XVE left ventricular assist system. ASAIO J 2007;53:298-303.

201. McCarthy PM, Smedira NO, Vargo RL, et al. One hundred patients with the HeartMate left ventricular assist device: evolving concepts and technology. J Thorac Cardiovasc Surg 1998;115:904-12.

202. Zierer A, Melby SJ, Voeller RK, et al. Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. Ann Thorac Surg 2007;84:515-20.

203. Frazier OH, Rose EA, Macmanus Q, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg 1992;53:1080-90.

204. Boyle AJ, Russell SD, Teuteberg JJ, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant 2009; 28:881-7.

205. Demirozu ZT, Etheridge WB, Radovancevic R, et al. Results of HeartMate II left ventricular assist device implantation on renal function in patients requiring post-implant renal replacement therapy. J Heart Lung Transplant 2011;30:182-7.

206. Haft J, Armstrong W, Dyke DB, et al. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. Circulation 2007;116:I8-I15.

207. John R, Pagani FD, Naka Y, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg 2010;140:174-81.

208. Long JW, Kfoury AG, Slaughter MS, et al. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. Congest Heart Fail 2005;11: 133-8.

209. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007; 357:885-96.

210. Morgan JA, John R, Rao V, et al. Bridging to transplant with the HeartMate left ventricular assist device: the Columbia Presbyterian 12-year experience. J Thorac Cardiovasc Surg 2004;127:1309-16.

211. Pagani FD, Long JW, Dembitsky WP, et al. Improved mechanical reliability of the HeartMate XVE left ventricular assist system. Ann Thorac Surg 2006;82:1413-8.

212. Slaughter MS, Sobieski MA, Gallagher C, et al. Low incidence of neurologic events during long-term support with the HeartMate XVE left ventricular assist device. Tex Heart Inst J 2008;35:245-9.

213. Hendry PJ, Mussivand TV, Masters RG, et al. The HeartSaver left ventricular assist device: an update. Ann Thorac Surg 2001;71:S166-70.

214. Slaughter MS, Sobieski MA 2nd, Tamez D, et al. HeartWare miniature axial-flow ventricular assist device: design and initial feasibility test. Tex Heart Inst J 2009;36:12-6.

215. Herrmann M, Weyand M, Greshake B, et al. Left ventricular assist device infection is associated with increased mortality but is not a contraindication to transplantation. Circulation 1997;95:814-7.

216. Aaronson KD, Eppinger MJ, Dyke DB, et al. Left ventricular assist device therapy improves utilization of donor hearts. J Am Coll Cardiol 2002;39:1247-54.

217. Patlolla V, Patten RD, Denofrio D, et al. The effect of ventricular assist devices on post-transplant mortality: an analysis of the United Network for Organ Sharing thoracic registry. J Am Coll Cardiol 2009;53:264-71.

218. Carrier M, Perrault LP, Bouchard D, et al. Effect of left ventricular assist device bridging to transplantation on donor waiting time and outcomes in Canada. Can J Cardiol 2004;20:501-4.

219. Burnett CM, Duncan JM, Frazier OH, et al. Improved multiorgan function after prolonged univentricular support. Ann Thorac Surg 1993;55: 65-71.

220. Stein ML, Robbins R, Sabati AA, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)-defined morbidity and mortality associated with pediatric ventricular assist device support at a single US center: the Stanford experience. Circ Heart Fail 2010;3: 682-8.

221. Russell SD, Rogers JG, Milano CA, et al. Renal and hepatic function improve in advanced heart failure patients during continuous-flow support with the HeartMate II left ventricular assist device. Circulation 2009;120:2352-2357.

222. Amir O, Delgado RM 3rd, Kar B, et al. Recovery from multi-organ failure in a patient with a continuous-flow left ventricular assist device. J Heart Lung Transplant 2005;24:1128-9.

223. Kirklin JK, Naftel DC, Kormos RL, et al. Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. J Heart Lung Transplant 2010;29:1-10.

224. Feldman CM, Khan SN, Slaughter MS, et al. Improvement in early oxygen uptake kinetics with left ventricular assist device support. ASAIO J 2008;54:406-11.

225. John R, Boyle A, Pagani F, et al. Physiologic and pathologic changes in patients with continuous-flow ventricular assist devices. J Cardiovasc Transl Res 2009;2:154-158.

226. John R, Lietz K, Schuster M, et al. Immunologic sensitization in recipients of left ventricular assist devices. J Thorac Cardiovasc Surg 2003; 125:578-91.

227. Kamdar F, Boyle A, Liao K, et al. Effects of centrifugal, axial, and pulsatile left ventricular assist device support on end-organ function in heart failure patients. J Heart Lung Transplant 2009;28:352-9.

228. Pagani FD, Dyke DB, Wright S, et al. Development of anti-major histocompatibility complex class I or II antibodies following left ventricular assist device implantation: effects on subsequent allograft rejection and survival. J Heart Lung Transplant 2001;20:646-53.

229. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-34.

230. Russo MJ, Hong KN, Davies RR, et al. Posttransplant survival is not diminished in heart transplant recipients bridged with implantable left ventricular assist devices. J Thorac Cardiovasc Surg 2009;138: 1425-32.

231. Slaughter MS. Outcomes of Medicare beneficiaries with ventricular assist devices. JAMA 2009;301:1657-8.

232. Vitali E, Lanfranconi M, Ribera E, et al. Successful experience in bridging patients to heart transplantation with the MicroMed DeBakey ventricular assist device. Ann Thorac Surg 2003;75:1200-4.

233. Ross H, Tinckam K, Rao V, et al. In praise of ventricular assist devices-mechanical bridge to virtual crossmatch for the sensitized patient. J Heart Lung Transplant 2010;29:728-30.

234. Cianci P, Lonergan-Thomas H, Slaughter M, et al. Current and potential applications of left ventricular assist devices. J Cardiovasc Nurs 2003; 18:17-22.

235. Daneshmand MA, Rajagopal K, Lima B, et al. Left ventricular assist device destination therapy versus extended criteria cardiac transplant. Ann Thorac Surg 2010;89:1205-9.

236. Haddad M, Lam K, Hendry P, et al. Left ventricular assist devices for the treatment of congestive heart failure. Curr Treat Options Cardiovasc Med 2005;7:47-54.

237. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation 2007;116:497-505.

238. MacIver J, Ross HJ, Delgado DH, et al. Community support of patients with a left ventricular assist device: the Toronto General Hospital experience. Can J Cardiol 2009;25:e377-81.

239. Stevenson LW, Miller LW, Desvigne-Nickens P, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004;110:975-81.

240. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723-30.

241. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001; 345:1435-43.

242. Moskowitz AJ, Weinberg AD, Oz MC, et al. Quality of life with an implanted left ventricular assist device. Ann Thorac Surg 1997;64: 1764-9.

243. Slaughter MS. Long-term continuous flow left ventricular assist device support and end-organ function: prospects for destination therapy. J Card Surg 2010;25:490-4.

244. Slaughter MS, Pagani FD, Rogers JG, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant 2010;29:S1-39.

245. Gazzoli F, Vigano M, Pagani F, et al. Initial results of clinical trial with a new left ventricular assist device (LVAD) providing synchronous pulsatile flow. Int J Artif Organs 2009;32:344-53.

246. Pagani FD. Continuous-flow rotary left ventricular assist devices with "3rd generation" design. Semin Thorac Cardiovasc Surg 2008;20: 255-63.

247. Pal JD, Klodell CT, John R, et al. Low operative mortality with implantation of a continuous-flow left ventricular assist device and impact of concurrent cardiac procedures. Circulation 2009;120:S215-9.

248. Slaughter MS, Naka Y, John R, et al. Post-operative heparin may not be required for transitioning patients with a HeartMate II left ventricular assist system to long-term warfarin therapy. J Heart Lung Transplant 2010;29:616-24.

249. Travis AR, Giridharan GA, Pantalos GM, et al. Vascular pulsatility in patients with a pulsatile- or continuous-flow ventricular assist device. J Thorac Cardiovasc Surg 2007;133:517-24.

250. Hendry PJ, Masters RG, Davies RA, et al. Mechanical circulatory support for adolescent patients: the Ottawa Heart Institute experience. Can J Cardiol 2003;19:409-12.

251. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.

252. Miller LW, Nelson KE, Bostic RR, et al. Hospital costs for left ventricular assist devices for destination therapy: lower costs for implantation in the post-REMATCH era. J Heart Lung Transplant 2006;25:778-84.

253. Russo MJ, Gelijns AC, Stevenson LW, et al. The cost of medical management in advanced heart failure during the final two years of life. J Card Fail 2008;14:651-8.

254. Alba AC, Rao V, Ivanov J, et al. Predictors of acute renal dysfunction after ventricular assist device placement. J Card Fail 2009;15:874-81.

255. Aslam S, Hernandez M, Thornby J, et al. Risk factors and outcomes of fungal ventricular-assist device infections. Clin Infect Dis 2010; 50:664-71.

256. Cowger J, Pagani FD, Haft JW, et al. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail 2010;3:668-74.

257. Drakos SG, Janicki L, Horne BD, et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. Am J Cardiol 2010;105:1030-5.

258. Fukamachi K, McCarthy PM, Smedira NG, et al. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181-4.

259. Genovese EA, Dew MA, Teuteberg JJ, et al. Incidence and patterns of adverse event onset during the first 60 days after ventricular assist device implantation. Ann Thorac Surg 2009;88:1162-70.

260. Kavarana MN, Pessin-Minsley MS, Urtecho J, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg 2002;73:745-50.

261. Kormos RL, Teuteberg JJ, Pagani FD, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist

device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg 2010;139:1316-13.

262. Lima B, Kherani AR, Hata JA, et al. Does a pre-left ventricular assist device screening score predict long-term transplantation success? A 2-center analysis. Heart Surg Forum 2006;9:E783-5.

263. Rao V, Oz MC, Flannery MA, et al. Revised screening scale to predict survival after insertion of a left ventricular assist device. J Thorac Cardiovasc Surg 2003;125:855-62.

264. Reinhartz O, Farrar DJ, Hershon JH, et al. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. J Thorac Cardiovasc Surg 1998;116:633-40.

265. Richartz BM, Radovancevic B, Frazier OH, et al. Low serum cholesterol levels predict high perioperative mortality in patients supported by a left-ventricular assist system. Cardiol 1998;89:184-8.

266. Robinson PJ, Billah B, Leder K, et al. Factors associated with deep sternal wound infection and haemorrhage following cardiac surgery in Victoria. Interact Cardiovasc Thorac Surg 2007;6:167-71.

267. Romano MA, Cowger J, Aaronson KD, et al. Diagnosis and management of right-sided heart failure in subjects supported with left ventricular assist devices. Curr Treat Options Cardiovasc Med 2010;12:420-30.

268. Schenk S, McCarthy PM, Blackstone EH, et al. Duration of inotropic support after left ventricular assist device implantation: risk factors and impact on outcome. J Thorac Cardiovasc Surg 2006;131:447-54.

269. Topkara VK, Dang NC, Barili F, et al. Predictors and outcomes of continuous veno-venous hemodialysis use after implantation of a left ventricular assist device. J Heart Lung Transplant 2006;25:404-8.

270. Anstadt MP, Hendry PJ, Plunkett MD, et al. Mechanical myocardial actuation during ventricular fibrillation improves tolerance to ischemia compared with cardiopulmonary bypass. Circulation 1990;82(suppl):IV284-90.

271. Anderson CA, Filsoufi F, Aklog L, et al. Liberal use of delayed sternal closure for postcardiotomy hemodynamic instability. Ann Thorac Surg 2002;73:1484-8.

272. Haddad M, Hendry PJ, Masters RG, et al. Ventricular assist devices as a bridge to cardiac transplantation: the Ottawa experience. Artif Organs 2004;28:136-41.

273. Hendry PJ, Masters RG, Mussivand TV, et al. Circulatory support for cardiogenic shock due to acute myocardial infarction: a Canadian experience. Can J Cardiol 1999;15:1090-4.

274. Matthews JC, Pagani FD, Haft JW, et al. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. Circulation 2010;121:214-20.

275. Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol 2009;54:312-21.

276. Slaughter MS. Hematologic effects of continuous flow left ventricular assist devices. J Cardiovasc Transl Res 2010;3:618-24.

277. Slaughter MS, Tsui SS, El-Banayosy A, et al. Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device. J Thorac Cardiovasc Surg 2007;133:1573-80.

278. Hendry PJ, Ascah KJ, Rajagopalan K, et al. Does septal position affect right ventricular function during left ventricular assist in an experimental porcine model? Circulation 1994;90:II353-8.

279. Matthews JC, Koelling TM, Pagani FD, et al. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163-72.

280. Kuhne M, Sakumura M, Reich SS, et al. Simultaneous use of implantable cardioverter-defibrillators and left ventricular assist devices in patients with severe heart failure. Am J Cardiol 2010;105:378-82.

281. Malani PN, Dyke DB, Pagani FD, et al. Successful treatment of vancomycin resistant Enterococcus faecium mediastinitis associated with left ventricular assist devices. Ann Thorac Surg 2003;76:1719-20.

282. Malani PN, Dyke DB, Pagani FD, et al. Nosocomial infections in left ventricular assist device recipients. Clin Infect Dis 2002;34:1295-1300.

283. Martin SI, Wellington L, Stevenson KB, et al. Effect of body mass index and device type on infection in left ventricular assist device support beyond 30 days. Interact Cardiovasc Thorac Surg 2010;11:20-3.

284. Meyer AL, Malehsa D, Bara C, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675-81.

285. Luckraz H, Woods M, Large SR. And hemolysis goes on: ventricular assist device in combination with veno-venous hemofiltration. Ann Thorac Surg 2002;73:546-8.

286. Bagdasarian NG, Malani AN, Pagani FD, et al. Fungemia associated with left ventricular assist device support. J Card Surg 2009;24:763-5.

287. Chinn R, Dembitsky W, Eaton L, et al. Multicenter experience: prevention and management of left ventricular assist device infections. ASAIO J 2005;51:461-70.

288. Eyler RF, Butler SO, Walker PC, et al. Vancomycin use during left ventricular assist device support. Infect Control Hosp Epidemiol 2009;30:484-6.

289. Gazzoli F, Grande AM, Pagani F, et al. Images in cardio-thoracic surgery: Novacor left ventricular assist device inflow valve endocarditis. Eur J Cardiothorac Surg 2009;35:910.

290. Grossi P, Dalla Gasperina D, Pagani F, et al. Infectious complications in patients with the Novacor left ventricular assist system. Transplant Proc 2001;33:1969-71.

291. Butany J, Leong SW, Rao V, et al. Early changes in bioprosthetic heart valves following ventricular assist device implantation. Int J Cardiol 2007;117:e20-3.

292. Feldman CM, Silver MA, Sobieski MA, et al. Management of aortic insufficiency with continuous flow left ventricular assist devices: bioprosthetic valve replacement. J Heart Lung Transplant 2006;25:1410-2.

293. Rao V, Slater JP, Edwards NM, et al. Surgical management of valvular disease in patients requiring left ventricular assist device support. Ann Thorac Surg 2001;71:1448-53.

294. Khan NA, Butany J, Zhou T, et al. Pathological findings in explanted prosthetic heart valves from ventricular assist devices. Pathology 2008;40:377-84.

295. Goldberg SG, Eckman P, Vanhaecke J. International Socieity for Heart and Lung Transplantation Google Chat page. Available at: http://groups.google.com/group/ishlt-hf/topics. Accessed January 29, 2011.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *The Canadian Journal of Cardiology* at http://onlinecjc.ca/, and at doi:10.1016/j.cjca.2011.03.011.