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

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The Canadian Cardiovascular Society published a comprehensive set of recommendations on the diagnosis and management of heart failure in January 2006. Based on feedback obtained through a national program of heart failure workshops and through active solicitation of stakeholders, several topics were identified because of their importance to the practicing clinician. Topics chosen for the present update include best practices for the diagnosis and management of right-sided heart failure, myocarditis and device therapy, and a review of recent important or landmark clinical trials. These recommendations were developed using the structured approach for the review and assessment of evidence adopted and previously described by the Society. The present update has been written from a clinical perspective to provide a user-friendly and practical approach. Specific clinical questions that are addressed include: What is right-sided heart failure and how should one approach the diagnostic work-up? What other clinical entities may masquerade as this nebulous condition and how can we tell them apart? When should we be concerned about the presence of myocarditis and how quickly should patients with this condition be referred to an experienced centre? Among the myriad of recently published landmark clinical trials, which ones will impact our standards of clinical care? The goals are to aid physicians and other health care providers to optimally treat heart failure patients, resulting in a measurable impact on patient health and clinical outcomes in Canada.

Key Words: *Congenital heart disease; Consensus statement; Device therapy; Diagnosis; Drug therapy; Etiology; Guidelines; Heart failure; Myocarditis; Prognosis; Pulmonary hypertension; Right-sided heart failure*

Mise à jour 2009 des Lignes directrices de la Conférence consensuelle de la Société canadienne de cardiologie sur l'insuffisance cardiaque : Diagnostic et prise en charge de l'insuffisance cardiaque droite, la myocardite, dispositifs thérapeutiques et récentes études cliniques importantes

La Société canadienne de cardiologie avait publié un ensemble complet de recommandations sur le diagnostic et la prise en charge de l'insuffisance cardiaque en janvier 2006. Selon les commentaires obtenus par l'entremise d'un programme national d'ateliers sur l'insuffisance cardiaque et par une sollicitation active des principaux intéressés, plusieurs thèmes ont été jugés importants pour le praticien. Les thèmes retenus pour la présente mise à jour incluent : les pratiques optimales en matière de diagnostic et de prise en charge de l'insuffisance cardiaque droite, de la myocardite et des dispositifs thérapeutiques et une revue des récentes études cliniques importantes ou déterminantes. Ces recommandations ont été rédigées avec une approche structurée pour l'analyse et l'évaluation des preuves que la Société a adoptées et décrites précédemment. Cette mise à jour a été rédigée d'un point de vue clinique pour plus de convivialité et de commodité. Les questions cliniques spécifiquement abordées sont notamment : Qu'est-ce que l'insuffisance cardiaque droite et comment approche-t-on les épreuves diagnostiques? Quelles autres entités cliniques peuvent prendre l'aspect de cette maladie nébuleuse et comment les distinguer? Quand doit-on s'inquiéter de la présence de myocardite et avec quelle rapidité les patients atteints de cette maladie doivent-ils être adressés vers un centre spécialisé? Parmi la myriade d'essais cliniques déterminants publiés récemment, lesquels auront un impact sur nos normes de soins cliniques? Les objectifs sont d'aider les médecins et autres professionnels de la santé à traiter de manière optimale les patients atteints d'insuffisance cardiaque, de manière à exercer un impact mesurable sur leur santé et sur le pronostic clinique de la maladie au Canada.

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In 2006, the Canadian Cardiovascular Society (CCS) published comprehensive guidelines on the diagnosis and management of heart failure as part of a commitment to a multi-year, closed-loop initiative designed to assist in the overall support of best practices for heart failure nationwide (1). In concert with these guidelines, the CCS implemented the National Heart Failure Workshop Initiative, a series of heart failure workshops held across the country to interactively discuss how to implement those guidelines and, through needs assessment, to identify additional challenges facing physicians and other health care providers in their day-to-day management of patients with heart failure. Feedback from these sessions, together with specific solicited input from key stakeholders, led to other important topics covered in the 2007 (2) and 2008 (3) updates. Topics covered in the 2007 update included treatment of heart failure during intercurrent illness, acute decompensation of heart failure and the use of biomarkers such as B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP). In 2008, topics included issues such as transfer and transition of heart failure care, and the diagnosis, investigation and management of specific cardiomyopathies. In many of these areas, there are few randomized clinical trials; therefore, many of the recommendations and practical tips are based on consensus.

The authors of the present update are the Primary Panel members who were responsible for identifying the scope of the present review, reviewing the literature, determining the relevance and strength of evidence, and formulating recommendations, which were agreed to by consensus. The Secondary Panel members represented a broad spectrum of Canadian practitioners and reviewed the paper, providing constructive feedback to the Primary Panel. The systematic review strategy and methods for formulating the recommendations are described in more detail on the CCS Heart Failure Consensus Conference Program Web site (www.hfcc.ca).

The objective of the CCS Heart Failure Consensus Conference 2009 update is to provide Canadian practitioners with recommendations and advice in two important and complex areas: right-sided heart failure (RHF) and myocarditis. Each of these topics are approached from a clinical perspective and are divided into five sections: What is it? When should I suspect it? How do I diagnose it? How should I treat it? When should I refer? Many of the conditions described in the current CCS guidelines update refer to uncommon or even rare entities, (ie, congenital heart disease and primary pulmonary arterial hypertension [PAH]) for which established subspecialty care and guidelines for care have been developed. The 2009 CCS heart failure update is intended to complement rather than replace these guidelines. Therefore, where appropriate, recommendations for the referral of patients afflicted with these conditions are included. In addition, recent clinical trials of importance, particularly those that lead to a change in recommendations or the development of new recommendations, are highlighted.

Once again, individuals from all relevant professional groups are represented in the current update. They include the following organizations: Canadian Pharmacists Association, Canadian Council of Cardiovascular Nurses, Canadian Geriatrics Society, Canadian Society of Internal Medicine, College of Family Physicians of Canada, and Canadian Association of Advanced Practice Nurses. The CCS Heart Failure Consensus Conference update 2009 has been developed for those seeking evidence-based recommendations for optimal heart failure care in Canada including cardiovascular specialists, internists, general practitioners, allied health care professionals, patients and families.

An extensive dissemination and implementation program has been developed for the CCS Heart Failure Consensus Conference Program. In addition to the CCS National Heart Failure Workshop Initiative, bilingual versions of a handy 'pocket card' and slide kit have been developed based on the 2006 to 2008 recommendations, and are available online. Details regarding these and other initiatives can be found on the CCS Heart Failure Consensus Conference Program Web site (http://hfcc.ca/index.aspx).

The class of recommendation and the grade of evidence were determined as follows:

Class I: Evidence or general agreement that a given procedure or treatment is beneficial, useful and effective.
Class II: Conflicting evidence or a divergence of opinion about the usefulness or efficacy of the procedure or treatment.
Class IIa: Weight of evidence is in favour of usefulness or efficacy.
Class IIb: Usefulness or efficacy is less well established by evidence or opinion.
Class III: Evidence or general agreement that the procedure or treatment is not useful or effective and, in some cases, may be harmful.
Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B: Data derived from a single randomized clinical trial or nonrandomized studies.
Level of evidence C: Consensus of opinion of experts and/or small studies.

RHF

Recommendations

- RHF should be considered in patients with unexplained symptoms of exercise intolerance or hypotension in combination with evidence of elevated jugular venous pressure, peripheral edema, hepatomegaly or any combination of these findings (class I, level C).
- If RHF is suspected, an echocardiogram should be performed to assess cardiac structure and function, and inferior vena cava distensibility (class I, level C).
- In cases of refractory RHF, or when the diagnosis is not clear, hemodynamic assessment with complete right heart catheterization should be considered (class I, level C).
- Annual flu shot is recommended (class I, level C).
- Antibiotic prophylaxis against infective endocarditis (IE) is recommended for patients at high risk (class I, level C).

Practical tips

- A complete history and physical examination is essential for patients with suspected RHF to plan further investigations and formulate a treatment plan.
- Atrial septal defect may be difficult to diagnose and should always be suspected in the setting of unexplained RHF or right ventricular (RV) enlargement. Bubble study or transesophageal echocardiography may be required for diagnosis.
- Judicious diuretic therapy should be considered for patients with symptomatic RHF, with a goal of euvolemia if feasible and tolerated.
- Patients with RHF may not have increased left atrial filling pressures and may be more sensitive to change in reduction of cardiac preload. This may manifest as light-headedness or elevation of serum creatinine. Careful monitoring of volume status is necessary.
- Patients with RHF may require increased doses of diuretics, which may lead to increased likelihood of hypokalemia. Judicious use of potassium-sparing diuretics may be useful in the maintenance of potassium homeostasis.

What is it?

RHF is a clinical syndrome that occurs when the right ventricle, due to systolic and/or diastolic dysfunction, is unable to produce adequate cardiac output for the needs of the individual, or is unable to do so with normal filling pressures. RHF may occur as pure right-sided failure (uncommon), or in association with left-sided heart failure (LHF) (common). Recent reviews and working groups describe, in detail, normal and abnormal function and disease states of the right ventricle beyond the scope of the present document (4-6). For RHF to be diagnosed, at least two features should be present: signs and symptoms consistent with RHF; and objective evidence of abnormal right-sided cardiac structure or function or elevated intracardiac pressures.

In general, RHF may be considered in terms of etiology (Tables 1 and 2).

Several specific clinical conditions, such as acute RV infarction (7), primary PAH (8) or congenital heart disease of moderate or severe complexity (9), that may cause RHF have been extensively described and are dealt with in detail in other published guidelines. The review will not address the specific problem of postcardiotomy RHF. The present guideline addresses the generic issue of the recognition and practical management of RHF.

When should I suspect it?

The clinical presentation of RHF is variable but typically involves exercise limitation, fatigue and evidence of systemic venous congestion. This will fall into three general categories:

1. Fluid retention (eg, ascites, peripheral edema, anasarca).
2. Exercise intolerance and fatigue (eg, low cardiac output, diastolic and systolic dysfunction).
3. Hypotension (especially with atrial and ventricular arrhythmias, and low cardiac output).

In addition, gastrointestinal symptoms, including anorexia, bloating, nausea and constipation, may be present and are common in the advanced stages of heart failure. There are also several conditions that may give rise to the suspicion of RHF, including liver cirrhosis, nephrotic syndrome and renal failure with significant volume overload. These conditions should be excluded before ascribing the clinical presentation as primarily due to RHF.

The underlying pathophysiology of RHF may include venous congestion, RV enlargement, increased pulmonary artery pressures and tricuspid or pulmonary valvular dysfunction. These are, in turn, confirmed by several physical examination findings. Most often, an abnormal jugular venous pressure is seen, which may represent reduced RV compliance and/or venous hypertension. In more severe cases, pitting sacral or peripheral edema will be present as liver enlargement, tenderness and even ascites. RV enlargement is manifest through a palpable impulse (lift or heave) present along the left sternal border, while a palpable pulmonary artery pulsation at the left upper sternal border may be present in the setting of significant pulmonary artery dilation. With PAH, the pulmonary valvular closure sound (P2) may be delayed, resulting in increased splitting of the second heart sound, or increase in intensity or even palpable. If pulmonary regurgitation is present with normal pulmonary pressure, a low-pitched and variable-length pulmonary decrescendo murmur may be present at the left sternal border. In the setting of pulmonary hypertension, a high-pitched Graham Steell's murmur is heard. Tricuspid regurgitation, when audible, is usually heard as a regurgitant-type murmur heard at the left lower sternal border. A right-sided S3 may be present and increases with inspiration, as do nearly all right-sided heart sounds, extracardiac sounds and murmurs. Tables 3 and 4 include several clinical and diagnostic abnormalities associated with RHF with or without pulmonary hypertension.

How do I diagnosis it?

RV dysfunction can be confirmed by imaging techniques. Typically, transthoracic echocardiography (TTE) is the primary modality chosen because it provides detailed anatomical and functional information about both ventricles, cardiac valves, pulmonary artery pressure, inferior vena cava distensibility and pericardium. Echocardiography laboratories should follow the recommendations provided by the Canadian Society of Echocardiography (http://www.csecho.ca/pdf/2004_Echo_Standards.pdf).

Standard measurements include right atrial (RA) and RV diameter, RV function, and estimates of RA and RV pressure, pulmonary artery pressure. Reference measurements are available at http://www.asecho.org/freepdf/ChamberQuantification.pdf. Echocardiography can estimate the RV systolic blood pressure (BP) and pulmonary artery systolic BP, having shown a correlation with measurements obtained at right heart catheterization in experienced echocardiography laboratories. RV systolic BP is considered normal if it is lower than 35 mmHg and increases with age and body mass (10); pulmonary artery systolic pressure is considered mildly abnormal between 36 mmHg and 50 mmHg, moderately abnormal between 51 mmHg and 75 mmHg and severely abnormal if higher than 75 mmHg. Cardiac magnetic resonance imaging (CMR) also provides a good assessment of the above measures, although relatively few centres with adequate experience and expertise are available. A multigated acquisition scan (MUGA) may also be used for the assessment of RV ejection fraction. Right heart catheterization for hemodynamic assessment is often necessary and can provide key information regarding pulmonary pressures, especially for pulmonary vascular resistance, which is a critical component for the assessment of PAH.

TABLE 1
Causes of right-sided heart failure (RHF)

Increased afterload, including left-sided heart failure and pulmonary arterial hypertension
Right ventricular (RV) myopathic process, RV infarction and restrictive heart disease
Right-sided valvular heart disease
Congenital heart disease including surgical residua
Pericardial disease (a mimic of RHF)

How should I treat it?

Very few randomized studies have been devoted to the problem of RHF. However, a few basic principles for the management of RHF can be stated. First, the diagnosis should be confirmed, and the reason for RHF established. Therapeutic options are guided by the underlying diagnosis. Generally, diuretics are the mainstay of therapy. Because patients with RHF may have normal or even low left ventricular (LV) filling pressures, cautious use of diuretics is mandatory, as excessive diuresis can result in prerenal azotemia, hypotension and exacerbation of arrhythmias. As such, it is not uncommon to see combination diuretic therapy to avoid excessive potassium loss or alkalosis. If severe pulmonary hypertension is present, efforts to avoid systemic hypotension are essential because it can lead to RV ischemia, worsening RV systolic performance and further hypotension. An annual flu shot is recommended for these patients, while endocarditis prophylaxis is only recommended for those at very high risk, including those with cyanotic heart disease, prosthetic intracardiac material or valves, and those with previous endocarditis (11,12).

RHF as a consequence of left-sided heart failure

Recommendation

- Patients with RHF secondary to or in association with LHF should be managed as per LHF (class I, level A).

Practical tip

- Carefully selected patients with advanced heart failure and severe pulmonary hypertension while on optimal therapy may be considered for therapy with sildenafil for improvement of symptoms and exercise tolerance.

The most common manifestation of RHF occurs in the setting in which pulmonary venous congestion is due to LHF. When LV dysfunction is present, patients typically exhibit features of both RHF and LV failure, although features of LV failure usually predominate. In this case, there are six principal mechanisms by which RHF can occur: pulmonary venous and secondary pulmonary arterial hypertension leads to increased RV afterload; a similar myopathic process occurs in the left and right ventricle; RV ischemia due to coronary disease; decreased coronary perfusion due to systemic hypotension; ventricular interdependence; and LV dilation resulting in RV diastolic dysfunction in a limited pericardial compartment (6).

The treatment of these conditions has been described in previous CCS heart failure guideline updates (1). However, in a minority of patients, right-sided features predominate. Even in this situation, elevation of LV filling pressures is still most likely and will drive treatment.

TABLE 2
Comparison of right-sided heart failure (RHF) by etiology

Cause	Clinical presentation	Differentiating features
Secondary to LV failure	Typical heart failure presentation	Abnormal LV valves with evidence of increased filling pressures
	Hypoxia in advanced stages	Can confirm via left heart or transeptal catheterization
		High BNP when decompensated
Secondary to PAH	RHF	Evidence of pulmonary hypertension
	Hypoxia may occur earlier	No evidence of increased LV filling pressures
	Evidence of significant lung disease may be present	May require cardiac catheterization to determine LV filling pressures
	Findings of pulmonary hypertension may be present	BNP may be modestly elevated
	Clinical findings may reflect the presence of conditions associated with PAH such as scleroderma	
Secondary to RV myopathic process	RHF	Diagnosis can usually be made on clinical grounds and with echocardiography or CMR
RV infarction	Acute or post-MI presentation	May need urgent right heart catheterization to determine RV and LV filling pressures
	May also have LV failure	Low cardiac output despite elevated JVP following acute MI
		May not tolerate vasodilator therapy due to systemic hypotension
ARVC	Familial, uncommon (10%) LV involvement, may be asymptomatic	–
Other rare cardiomyopathy*	Variable	–
Restrictive cardiomyopathy	RHF	Pulmonary hypertension may be present
	May mimic constriction	BNP may be very high
	Mixed RV/LV failure	
Pericardial disease†	RHF without evidence of pulmonary hypertension	Pulmonary hypertension absent
		May see abnormal pericardium
		May differentiate from restrictive cardiomyopathy by tissue Doppler assessment
		Cardiac catheterization and/or RV biopsy may be required for differentiation
Right-sided valvular heart disease	Clinical findings of pulmonary or tricuspid valve disease	Evidence of severe valvular structural and functional abnormality
		Usually observed by echocardiography
	Associated condition present (eg, endocarditis, carcinoid, diet pill ingestion)	Evidence of interference of tricuspid closure by pacing wire, long history of RV pacing, with no other cause for ventricular dysfunction
	History of RV pacing	
Congenital heart disease	Highly variable but, frequently, a history of congenital heart disease precedes RHF presentation	Congenital heart disease noted by echocardiography or CMR
		Unexplained increase in RV volume warrants careful evaluation to rule out atrial septal defect or other intracardiac shunt; transesophageal echocardiography may be necessary

**Uhl's anomaly, Chagas' disease (uncommon in North America, common elsewhere), right-sided involvement of hypertrophic cardiomyopathy; †Mimic of RHF. ARVC Arrhythmogenic right ventricular cardiomyopathy; BNP B-type natriuretic peptide; CMR Cardiac magnetic resonance imaging; JVP Jugular venous pressure; LV Left ventricle; RV Right ventricle; MI Myocardial infarction; PAH Pulmonary arterial hypertension*

Therefore, any patient presenting with RHF must undergo careful determination of the presence of LV failure. Recent data (13-15) suggest that patients with pulmonary hypertension that is out of proportion to the elevation in left-sided filling pressures may benefit from the addition of phosphodiesterase inhibitors, such as sildenafil, to improve symptoms and exercise tolerance. However, patients should display evidence of ongoing pulmonary hypertension with advanced symptoms in the face of established optimal medical therapy before sildenafil use is considered. In addition, they should ideally be referred to a centre with experience and expertise in the management of heart failure.

In particular, patients with congenital heart disease may present with RHF due to a wide variety of specific anomalies or surgical residua. When identified, these patients should be referred to an adult congenital heart disease centre (9). Given the rapidly expanding percutaneous and surgical options for patients with lesions such as isolated atrial septal defect, referral is suggested when they are associated with heart failure.

RHF as a consequence of cor pulmonale and PAH

Recommendations

- Cor pulmonale is RHF caused by PAH, which is usually a consequence of lung disease. Cor pulmonale should be suspected in patients with PAH or lung disease who also have signs and/or symptoms of RHF (class 1, level C).
- Patients with PAH should be evaluated in centres with experience and expertise in the management of this disorder (class 1, level C).
- Vasodilator treatment for chronic PAH (with or without cor pulmonale), should be considered with calcium channel blockers, phosphodiesterase inhibitors, endothelin antagonists or prostacyclin analogues. These therapies should be instituted by clinicians with experience in the management of PAH (class 1, level B).
- Anticoagulation with warfarin should be considered for most patients with primary PAH (class IIa, level C).

Practical tips

- Ventilation/perfusion lung scanning, pulmonary angiography and chest computed tomography (CT) can be used to diagnose acute and chronic pulmonary thromboembolism as the cause of cor pulmonale.
- Radionuclide ventriculography, CMR and/or an echocardiography can be used to noninvasively determine RV ejection fraction and other measures of RV function.
- Pulmonary function testing with diffusion of carbon monoxide should be performed to determine underlying obstructive or interstitial lung disease.

- Complete right-heart cardiac catheterization should be considered to diagnose and quantify PAH.
- Lung biopsy may be considered for diagnosis in cases in which the diagnosis is in doubt and will refine treatment.
- Evaluation for lung and heart-lung transplantation should be considered for end-stage cor pulmonale.

What is it?

Cor pulmonale is defined as RV enlargement and dysfunction caused by a primary or secondary pulmonary pathology in association with pulmonary hypertension (defined as a mean pulmonary arterial pressure higher than 25 mmHg). Pathophysiological mechanisms causing pulmonary hypertension include pulmonary vasoconstriction, anatomical compromise of the pulmonary vascular bed secondary to lung disorders, increased blood viscosity and idiopathic primary pulmonary hypertension. This results in increased pulmonary arterial pressure, increased RV afterload resulting in RV dilation, and reduced function. Determination of the etiological factor (Table 3) is of utmost importance because several therapies specific to the underlying cause have been developed. For these reasons, patients with heart failure and PAH (without LV failure) should be referred to centres with experience and expertise in the management of this disorder.

How do I diagnose it?

Identification of patients with cor pulmonale should be suspected in patients with either lung disease or PAH, and signs and symptoms of RHF (Table 4).

Once cor pulmonale is suspected, testing should be directed toward the suspected etiology. Typically, this would include an electrocardiogram (ECG), chest x-ray, echocardiography (with a specific request for evaluation of RV function, pulmonary pressures and left-to-right shunting), ventilation/perfusion scan, pulmonary function tests (with diffusion of carbon monoxide) and CT of the chest. Coronary angiography with right-sided and pulmonary pressures may be required for diagnostic testing, but also to aid therapeutic options based on the reversible nature of pulmonary hypertension. Rarely, lung biopsy is required to determine the underlying etiology of pulmonary hypertension. Laboratory markers used for diagnostic purposes are summarized in the 2008 CCS guidelines (3).

How should I treat it?

Therapeutic options for PAH and cor pulmonale are specific to the causal etiology and are summarized by other international guidelines (8,16). Therapeutic options should be assessed at centres with appropriate expertise. Generally, the focus is on treating underlying pulmonary disease, improving oxygenation, improving RV function and decreasing pulmonary vasoconstriction. The use of oxygen, vasodilators, positive inotropic agents and anticoagulants are key therapies. In cor pulmonale, diuretics can result in the relief of symptoms; however, over-diuresis can lead to excessive volume depletion resulting in a decline in cardiac output. Anticoagulation with warfarin is recommended in patients at high risk for thromboembolism. Drugs specific to therapy include calcium channel blockers, sildenafil, epoprostenol, treprostinil, bosentan and iloprost. Lung and heart-lung transplantation can be considered for end-stage cor pulmonale.

TABLE 3
Classification of pulmonary hypertension as advanced at the World Symposium on Primary Pulmonary Hypertension

Pulmonary arterial hypertension
Primary pulmonary hypertension
Sporadic disorder
Familial disorder
Related conditions
Collagen vascular disease
Congenital systemic-to-pulmonary shunt
Portal hypertension
HIV infection
Drugs and toxins
Anorectic agents (appetite suppressants)
Others
Persistent pulmonary hypertension of the newborn
Others
Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Extrinsic compression of central pulmonary veins
Fibrosing mediastinitis
Adenopathy and/or tumours
Pulmonary veno-occlusive disease
Others
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitudes
Neonatal lung disease
Alveolar-capillary dysplasia
Others
Pulmonary hypertension resulting from chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
In situ thrombosis
Sickle cell disease
Pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature
Inflammatory conditions
Schistosomiasis
Sarcoidosis
Others
Pulmonary capillary hemangiomatosis

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RHF due to valvular disease

Recommendations

- Cardiologist referral should be offered to patients with a right-sided obstructive lesion and to patients with a moderate or severe regurgitant right-sided lesion for assessment of etiology, associated diseases and treatment plan (class I, level C).
- Patients with severe right-sided obstructive valvular heart disease should undergo evaluation at a centre with expertise and experience in the management of this condition (class I, level C).
- Endocarditis prophylaxis should be prescribed for appropriate indications in those at high risk for IE, such as patients with previous IE, prosthetic valves or conduits, or cyanotic congenital heart disease (class I, level C).
- Referral for consideration of surgical (repair or replacement) or percutaneous palliation of right-sided valvular dysfunction should be offered to patients with symptoms of RHF despite medical therapy (class I, level B).
- Patients with severe (gradient higher than 80 mmHg) or symptomatic moderate (gradient 50 mmHg to 79 mmHg) pulmonary valvular

TABLE 4
Common symptoms, signs and test results in right-sided heart failure (RHF) without pulmonary hypertension and in cor pulmonale

Common features	RHF without pulmonary hypertension	Cor pulmonale
Symptoms	Fatigue	Fatigue
	Hepatic congestion	*Hemoptysis*
	Right upper quadrant discomfort	*Hoarseness*
	Anorexia/early satiety	Hepatic congestion
	Peripheral edema	Right upper quadrant discomfort
	Cough	Anorexia/early satiety
	Shortness of breath/orthopnea*	Peripheral edema
		Cough
		Shortness of breath/orthopnea*
Physical signs	Elevated jugular venous pulsation, positive hepatojugular reflux or Kussmaul's sign	Elevated jugular venous pulsation, positive hepatojugular reflux or Kussmaul's sign
	Peripheral or sacral edema	Peripheral or sacral edema
	Ascites	Ascites
	Hepatomegaly or liver tenderness	Hepatomegaly or liver tenderness
	Right-sided third heart sound	Right-sided third heart sound, *increased pulmonary closure sound, pulmonary ejection click*
	Murmur of tricuspid regurgitation	Murmur of tricuspid regurgitation
	Signs of right ventricular enlargement	Signs of right ventricular enlargement
		Evidence of coexisting underlying pulmonary cause of cor pulmonale
Diagnostic testing	ECG: Right axis deviation, right ventricular hypertrophy, p pulmonale pattern low-voltage QRS, incomplete or complete right bundle branch block	ECG: Right axis deviation, right ventricular hypertrophy, p pulmonale pattern low-voltage QRS, incomplete or complete right bundle branch block
	Chest x-ray: Right-sided cardiac enlargement, enlargement of pulmonary arteries (uncommon), oligemic peripheral lung fields (rare), right-sided pleural effusion*	Chest x-ray: Right-sided cardiac enlargement, enlargement of pulmonary arteries, *oligemic peripheral lung fields*, right-sided pleural effusion*
	Echocardiography: Evidence of abnormal right ventriular structure and/or function. No evidence of increased pulmonary pressure. *Septal flattening during diastole but not systole*	Echocardiography: Evidence of abnormal right ventricular structure and/or function. *Evidence of increased pulmonary pressure. Septal flattening during systole*

*Items appearing in italics occur in the setting of cor pulmonale but are very uncommon in its absence. *Less commonly found, but may occur. ECG Electrocardiogram*

stenosis should be referred or considered for balloon valvuloplasty or surgical intervention (class I, level B).

- In the case of surgical right-sided valvular replacement, a bioprosthesis is usually preferred over a metallic valve (class I, level B).
- Surgical intervention may be considered in cases of severe tricuspid regurgitation with structural deformity of the valve (eg, Epstein's anomaly), endocarditis with valve destruction, or when ventricular dilation is severe and uncontrolled with medical therapy (class IIa, level C).

Practical tips

- Right heart catheterization may be required to quantify the severity of pulmonary stenosis, or to assess for pulmonary hypertension as a cause of a valvular lesion.
- Right-sided valvular heart disease, especially pulmonic valvular or infundibular stenosis, is frequently congenital in origin; therefore, assessment for other congenital anomalies is essential.
- Patients with trivial (mean gradient lower than 25 mmHg) or mild (gradient lower than 50 mmHg) pulmonary stenosis require no intervention or exercise limitation, but should have periodic follow-up (approximately every five years).
- Patients with right-sided valvular stenosis may have underlying carcinoid syndrome or ingestion of appetite suppressants.

What is it?

Uncommonly, right-sided valvular lesions can cause RHF. Typically, it is caused by valvular regurgitation (pulmonary insufficiency or tricuspid insufficiency) or stenosis (pulmonary stenosis). Pulmonary and tricuspid regurgitation are most commonly caused by secondary pulmonary hypertension, whereas pulmonary stenosis is congenital. Other etiologies include IE, tetralogy of Fallot following surgical repair, carcinoid heart disease, syphilis, dilation of the pulmonary trunk in Marfan syndrome or Takayasu arteritis, medications (methysergide, pergolide, fenfluramine), trauma from right heart instrumentation, as a complication related to therapeutic balloon catheter dilation of a stenotic pulmonic valve, or as a separate congenital defect.

Increasingly, RV pacing has been associated with both RHF and LHF (17). This has been thought to be related to iatrogenic ventricular dyssynchrony and gradual loss of biventricular function. One pilot study (18) showed improved symptoms and ventricular function when biventricular pacing was instituted in patients with presumed RV pacing-induced LV failure. In addition, case reports suggest that right-sided pacemaker wires may entrap or perforate the tricuspid valve, presenting with severe insufficiency (or even stenosis) and isolated RHF (19,20). Tricuspid insufficiency may also occur following RV biopsy, presumably as a result of damage to the chordae and loss of tricuspid valve coaptation (21).

How do I diagnose it?

Primary valvular RHF should be considered if there is a documented structural abnormality and severe dysfunction (regurgitation, stenosis or both) of the tricuspid or pulmonary valve, and no other identified condition responsible for these findings (such as left-sided rheumatic valvular heart disease or pulmonary hypertension). Initial testing will include chest x-ray, ECG and echocardiography assessment. Subsequent testing will depend on which clinical or diagnostic abnormalities are seen, such as CMR, chest CT, angiography or hemodynamic monitoring.

How do I treat it?

Treatment will depend on the underlying valvular disorder. In general, IE prophylaxis and treatment should follow the recommendations of the American Heart Association (11,12). Coexisting pulmonary hypertension should be managed in the usual fashion. Pulmonary stenosis should be managed according to the pressure gradient determined at right-heart catheterization.

When should I refer the patient?

Patients with underlying right-sided valvular lesions and RHF should be examined by a specialist with expertise and experience in the diagnosis and assessment of right-sided valvular heart disease. This may include surgical consultation after the initial visit.

Arrhythmogenic RV cardiomyopathy

Recommendations

- Arrhythmogenic RV cardiomyopathy (ARVC) should be suspected in individuals with unexplained dilation or dysfunction of the right ventricle in whom there is a history of ventricular arrhythmia, syncope or heart failure, or in whom characteristic ECG changes or a positive family history of ARVC is noted (class I, level C).
- All patients in whom ARVC is suspected should be assessed for European Society of Cardiology (ESC)/International Society and Federation of Cardiology criteria to establish a diagnosis (class I, level C).
- Echocardiography or CMR should be performed as part of a diagnostic workup in all patients suspected to have ARVC (class I, level B).
- Individuals with ARVC should avoid strenuous or high-intensity sports activities (class I, level B).
- An implantable cardioverter defibrillator (ICD) should be offered to all eligible patients with ARVC who have had a cardiac arrest or a history of sustained ventricular tachycardia (class I, level B).
- ICD may be considered for the prevention of sudden cardiac death (SCD) in eligible patients with ARVC in whom the risk of SCD is judged to be high (class IIa, level C).
- All patients with ARVC should be referred to a centre with experience and expertise in the management of this condition (class I, level C).

Practical tips

- Up to 40% of patients with ARVC may have a normal ECG on initial presentation, although almost all patients will develop pathological ECG changes within six years (22).
- Interpretation of CMR for ARVC should be performed at experienced centres. An abnormal scan in isolation is not diagnostic for ARVC.
- EMB of the RV free wall for ARVC should be performed with extreme caution and at an experienced centre due to the high risk of myocardial perforation and cardiac tamponade.
- Antiarrhythmic drugs or catheter ablation should not be used in the place of ICD therapy for patients with ARVC, but may be considered in patients who refuse or who are not candidates for device therapy.
- Genetic testing should be considered for families with ARVC for the purpose of screening and/or genetic counselling.

What is it?

ARVC or arrhythmogenic RV dysplasia (ARVD) is a rare cardiomyopathy characterized by fatty/fibrofatty replacement of the right, and sometimes left, ventricular myocardium. The prevalence of ARVC is estimated to be one in 1000 in the general population (23). The disease is most often diagnosed as an inherited disorder with an autosomal-dominant pattern and variable penetrance. At least 11 gene mutations, mostly of genes for cardiac desmosome, have been identified to cause ARVC (24).

When should I suspect it?

ARVC should be suspected in a patient with unexplained RV dysfunction, dilation or RHF, a history of ventricular tachyarrhythmia (particularly of left bundle branch block morphology) or syncope, characteristic ECG changes (eg, epsilon waves), a family history suggestive of syncope or sudden death, and in young people or athletes with a history of syncope or cardiac arrest during exercise or sports activities.

How do I diagnose it?

Clinical diagnosis is made based on the 1994 ESC/International Society and Federation of Cardiology joint task force criteria for ARVC, using a combination of functional, structural, histological, electrocardiographic and hereditary markers (25). Two major, one major and two minor, or four minor criteria are required for a diagnosis (Table 5). Palpitation, syncope (especially during exercise), atypical chest pain and dyspnea are the most common presenting clinical features of patients with ARVC (26), but in more than 20% of cases, sudden death can be the first sign of disease manifestation (27).

TTE and CMR are the imaging modalities of choice. CMR is highly sensitive for detecting intramyocardial fibrofatty changes typical of ARVC (28), and may be superior to TTE, especially when strict imaging criteria are adhered to (29). However, there is marked interobserver variability for abnormal CMR findings (29). The most characteristic echocardiography findings are increased RV outflow tract dimensions and abnormal RV morphology (30).

A histological diagnosis requires demonstration of total transmural fibro/fibrofatty replacement of the ventricular myocardium. EMB is only modestly sensitive (less than 70%) for detecting ARVC (31), particularly when biopsy samples are taken only from the interventricular septum rather than the RV free wall. Although both fatty and fibrous changes can be seen in other cardiomyopathies (eg, alcoholic and inherited cardiomyopathies), the triad of findings of more than 3% fatty tissues, more than 40% fibrous tissues and less than 45% residual myocytes in a sample strongly suggests a diagnosis of ARVC (31).

Presently, genetic testing for ARVC is not widely available and cannot be routinely recommended. It is most useful in confirming the disease in suspected cases when other diagnostic workups have been inconclusive. The pickup rate of known mutations among unrelated cases is only 30% (32); therefore, a negative test cannot be used to exclude the diagnosis.

How should I treat it?

The primary goal of treatment of ARVC is to reduce the risk of sudden arrhythmic death. The secondary goal of treatment is to manage symptoms of ventricular arrhythmias and RHF. To date, there have been no prospective randomized controlled trials to determine the efficacy of pharmacological and device therapies on the prevention of sudden death in ARVC; therefore, recommendations are based on anecdotal experience or observational studies of small cohorts. Regular heart failure therapy should be prescribed for patients with ARVC and heart failure. Cardiac transplantation is an option for eligible patients with end-stage ARVC and intractable heart failure or ventricular tachyarrhythmia.

In patients with ARVC who have had a cardiac arrest or a history of life-threatening ventricular arrhythmia (eg, sustained ventricular tachycardia), ICD use is associated with a very low subsequent risk of arrhythmic death (33) and should be considered in all eligible patients for the secondary prevention of SCD (34). Antiarrhythmic drugs, such as sotalol, may be used as adjuvant therapy for arrhythmia suppression (35). Catheter radiofrequency ablation may also be considered in patients with frequent ICD discharges for recurrent ventricular tachyarrhythmia, although long-term results have been disappointing (36).

The benefit of ICD for the primary prevention of SCD in ARVC is less clear, given the overall low mortality rate (lower than 3% per year) for the disease's natural history, and the observation that 30% of all deaths are sudden deaths (37). However, ICD may be considered for primary prevention in eligible patients who have one or more high-risk

TABLE 5
Diagnostic criteria* for arrhythmogenic right ventricular cardiomyopathy (ARVC)

Major criteria	Minor criteria
Severe dilation and reduction of right ventricular ejection fraction with no (or only mild) left ventricular impairment	Mild global right ventricular dilation and/or ejection fraction reduction with normal left ventricle
Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)	Mild segmental dilation of the right ventricle
Severe segmental dilation of the right ventricle	Regional right ventricular hypokinesia
Fibrofatty replacement of myocardium on endomyocardial biopsy	Inverted T waves in right precordial leads (V2 and V3) (people older than 12 years of age; in the absence of right bundle branch block)
Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1-V3)	Late potentials (signal averaged electrocardiogram)
Familial disease confirmed at necropsy or surgery	Left bundle branch block type ventricular tachycardia (sustained and nonsustained) (electrocardiogram, Holter monitor, exercise testing)
	Frequent ventricular extrasystoles (>1000/24 h) on Holter monitor
	Familial history of premature sudden death (<35 years of age) due to suspected ARVC
	Familial history (clinical diagnosis based on present criteria)

**Diagnosis requires the presence of two major, one major and two minor, or four minor criteria. Modified and reprinted with permission from reference 25*

factor (eg, extensive RV involvement, LV involvement, unexplained syncope) for SCD (34). Electrophysiology testing with programmed ventricular stimulation cannot reliably identify subsets of ARVC patients at high risk for SCD to require device therapy (33). Patients with mutations in *ARVD2* and *ARVD5* loci may also be at increased risk for SCD relative to other disease genotypes (38,39).

Management of athletes with ARVC represents a special challenge. In North America, ARVC is estimated to be the cause in less than 5% of all sudden deaths among young athletes (40). Because exercise can provoke the development of malignant ventricular tachyarrhythmia in ARVC, all athletes diagnosed with the disease should avoid strenuous or high-intensity competitive sports activities (41), even in those who are currently asymptomatic. The decision to participate in low-intensity (low static, low dynamic) sports activities (such as class IA sports as defined by the 36th Bethesda Conference) (42) may be individualized.

When should I refer the patient?

All patients with ARVC should be referred to experienced centres with electrophysiology services and genetic counselling. For families of patients with ARVC, genetic testing may be considered for screening and/or genetic counselling. Identification of gene carriers may allow targeted serial surveillance for early disease diagnosis (the so-called 'concealed' phase). However, the ethical implications of genotyping in the diagnosis of silent carriers requires further clarification.

Conditions that mimic RHF

Several conditions may mimic RHF, including nephrotic syndrome, liver failure with ascites, severe myxedema, chronic venous insufficiency and lymphedema. On close examination, these patients do not have evidence of increased right-sided filling pressures, or RV enlargement or dysfunction. Patients with severe airway obstruction may have elevated venous pressure. Echocardiography is a valuable adjunctive test to rule out significant cardiac disease. Furthermore, these patients will have another explanation for their presentation.

Constrictive pericarditis

Recommendations

- Constrictive pericarditis should be suspected in a patient with unexplained RHF (class 1, level C).
- CT scan or CMR should be performed in all patients with suspected constrictive pericarditis to assess for pericardial thickening (class 1, level B).
- Echocardiography with Doppler assessment of ventricular filling, as well as a right- and left-sided (simultaneous) cardiac catheterization (with manoeuvres if necessary) should be performed in all cases of constrictive pericarditis to confirm the presence of a constrictive physiology (class 1, level B).
- Surgical referral for pericardiectomy should be considered for patients with constrictive pericarditis and persistent advanced symptoms despite medical therapy (class 1, level B).
- Patients with symptomatic constrictive pericarditis should be offered referral to a centre with expertise in the management of this condition (class 1, level C).

Practical tips

- TTE is insensitive for detecting pericardial thickening but is a useful first test for examining constrictive physiology; transesophageal echocardiography may further improve the sensitivity over the transthoracic approach.
- When extensive calcification of the pericardium is present, CT may be more effective than CMR for measuring pericardial thickness.
- Provocation testing in the cardiac catheterization laboratory, such as rapid volume loading (eg, intravenous infusion of 1 L of normal saline over 6 min to 8 min) and simultaneous LV and RV measurement during respiration, may unmask hemodynamic signs of constriction in patients with early or occult forms of constrictive pericarditis.
- The diagnosis of pericardial constriction may be difficult and is made on clinical grounds with supporting information from diagnostic testing. Depsite extensive workup, information from endomyocardial biopsy (EMB) or even at open thoracotomoy may be required to assist in the diagnosis.

What is it?

Constrictive pericarditis is an uncommon disease caused by fibrosis and/or inflammation of the pericardium, resulting in impaired diastolic filling of the ventricles with or without reduced systolic function. In chronic constrictive pericarditis (the most common form), the pericardium is thickened, scarred and frequently calcified. However, up to 20% of cases may have normal pericardial thickness (43). At least six clinical forms of constrictive pericarditis have been described – transient, subacute, localized, occult, chronic and effusive-constrictive (44).

When should I suspect it?

Constrictive pericarditis should be suspected in patients with unexplained RHF in whom there is a history of pericardial disease or predisposing pericardial injury. Presentation is often indolent but progressive, and disease onset may occur years after the initial insult. The most frequent causes are idiopathic pericarditis, previous cardiac surgery, previous mediastinal radiation and, if from an area at risk, tuberculosis (45).

Less common causes include infection, drugs/toxins, neoplasm, connective tissue disease, recent myocardial infarction (often preceded by Dressler's syndrome), previous trauma and uremia, among others.

How do I diagnosis it?

The diagnosis is based on a combination of compatible clinical, imaging and hemodynamic findings (46). Chest x-ray may show pericardial calcification. CT and CMR are both sensitive tests for detecting pericardial thickening (greater than 2 mm to 4 mm) (47). When ordering the echocardiogram, the sonographer should be made aware in advance that the indication for testing is to assess for constrictive physiology. Simultaneous left- and right-sided cardiac catheterization may show equalization of diastolic pressures. These findings, however, are not specific for constriction, and they may be masked in the presence of atrial arrhythmia or coexisting cardiac pathology.

Differentiation between constrictive pericarditis and restrictive cardiomyopathy is particularly challenging. Traditional hemodynamic criteria for constriction obtained during cardiac catheterization are not reliable, and up to 25% of suspected cases may remain unclassified (48). Newer criteria that rely on the relative dynamic changes during respiration between RV and LV peak systolic pressures (49) or systolic pressure-time areas (50) often provide better discrimination (ie, ventricular discordance favours constriction). Other tests, such as tissue and colour M-mode Doppler imaging (51) or measurement of plasma BNP levels (52), may also aid in the differentiation.

Pericardial biopsy is not routinely recommended and is rarely helpful for ascertaining the etiology of the constriction. If obtained, however, mycobacterial and fungal culture of the biopsied tissue should be included.

How should I treat it?

Management includes treatment to relieve symptoms of RHF, control secondary arrhythmia (eg, atrial fibrillation) and provide timely surgical consultation for pericardiectomy. Any underlying cause of the pericardial injury, if found, should be promptly treated. Short courses of nonsteroidal anti-inflammatory drugs or corticosteroids may be considered in transient and subacute forms of constrictive pericarditis if an inflammatory component is thought to be present (53), such as early stages of tuberculous (54) or postoperative (55) constrictive pericarditis (53). Pericardiectomy should be considered for all symptomatic patients with acceptable surgical risks and reasonable life expectancy in whom there is persistent hemodynamic evidence of constriction. Current surgical mortality rates average 6% to 12% (56,57), but can be elevated further if there is coexisting myocardial damage, extensive pericardial calcification ('outer porcelain heart') or previous mediastinal radiation. Optimal timing for pericardiectomy is not known, although survival is lower among patients with more severe symptoms of heart failure at surgery (57,58).

When should I refer the patient?

All patients with constrictive pericarditis should be referred to experienced centres with advanced cardiac imaging, catheterization and surgical availability.

MYOCARDITIS

Recommendations

- Myocarditis should be suspected in the following clinical scenarios:
  - Cardiogenic shock due to LV systolic dysfunction (global or regional), where etiology is not apparent.
  - Acute or subacute development of LV systolic dysfunction (global or regional), where etiology is not apparent.
  - Evidence of myocardial damage not attributable to epicardial coronary artery disease or another cause (class I, level C).
- Referral to a centre with experience and expertise in the assessment and management of myocarditis should be considered for patients with suspected myocarditis (class I, level C).
- Urgent referral for evaluation/consideration for cardiac transplantation or mechanical circulatory support should be considered for patients with heart failure and evidence of resulting progressive clinical deterioration or end-organ dysfunction (class I, level C).
- Referral for further evaluation/consideration for transplantation or mechanical circulatory support should be considered for patients who remain in severe HF following implementation of standard HF therapy (class I, level C).
- Best medical therapy, including supportive care is recommended for the treatment of myocarditis (class I, level C).
- Routine use of general or specific immunological therapies directed toward myocarditis are not recommended, as this has not been shown to alter outcomes, and may lead to side effects or complications (class III, level B).
- Expert clinical follow-up is required until myocarditis is determined to be resolved or until a chronic management plan is in place (class IIa, level C).

Practical tips

- Clinical signs and symptoms of myocarditis may be highly variable. This may include presentations ranging from being similar to acute myocardial infarction to new-onset asymptomatic LV systolic dysfunction. Therefore, a high degree of clinical suspicion should be exercised.
- Other potential causes of cardiac dysfunction must be ruled out before a diagnosis of myocarditis can be made (eg, epicardial coronary artery disease, primary valvular disease, noninflammatory etiologies). At a minimum, this requires routine diagnostic evaluation for new-onset LV dysfunction (as per the 2006 CCS heart failure guidelines [1]). However, additional tests may include cardiac catheterization and CMR, with or without RV biopsy.
- Biomarker and 12-lead ECG findings in patients with myocarditis may mimic those of acute myocardial infarction or acute pericarditis.
- Patients with a response to therapy and evidence of resolution of cardiac dysfunction should have an expert clinical follow-up examination in three to six months to monitor and confirm clinical stability.
- Patients with persistence of heart failure symptoms or ventricular dysfunction should be followed in a multidisciplinary heart failure/function clinic, and referred to specialized centres when appropriate.
- Precise diagnostic criteria for acute myocarditis have not been prospectively validated, although two algorithms have been proposed: the Dallas (59,60) and Lake Louise criteria (61). These criteria consider four major elements in determining the potential for the presence of acute myocarditis. They are:
  1. Symptoms and clinical findings consistent with acute or recent myocardial damage.
  2. Evidence of cardiac structural abnormalities in the absence of a demonstrable epicardial coronary cause.
  3. Regional or global delayed enhancement or increased T2 signal on CMR.
  4. Presence of inflammatory cell infiltrate or positive viral genome signal on examination of EMB specimens.
- While routine diagnostic EMB is not required in most cases of suspected acute myocarditis, clinical conditions may arise in which knowledge of EMB results may be of value in the planning of potential mechanical ventricular support or cardiac transplantation. These include patients with new-onset heart failure (less than two weeks duration) with hemodynamic compromise, and in those presenting with subacute heart failure (two to 12 weeks), and any

of the following: high-grade heart block, recurrent ventricular arrhythmias or unresponsive to therapy.

- Evaluation of EMB samples should be performed by an experienced cardiac pathology laboratory. Evaluation of EMB for myocarditis should include the use of histopathological markers of inflammation and necrosis, immunohistochemical markers, and assessment for viral particles.

What is it?

Myocarditis is defined as 'inflammation of the heart muscle'. Classic myocarditis refers to inflammation of the heart muscle as a result of exposure to either discrete external antigen triggers, such as viruses, bacteria, parasites and drugs, or to internal triggers such as autoimmune activation against self-antigens.

When should I suspect it?

The diagnosis of myocarditis is challenging due to its varying clinical presentation, nonspecific symptoms and physical findings, and the lack of a sensitive and specific noninvasive diagnostic confirmatory test. Accordingly, a high level of clinical suspicion, together with a hybrid of clinical and laboratory criteria and new imaging modalities, may help to secure the diagnosis.

The clinical presentation may range from asymptomatic ECG or echocardiographic abnormalities, to symptoms mimicking acute myocardial infarction, to arrhythmias or heart failure, or to hemodynamic collapse. Classically, patients with myocarditis present with nonspecific symptoms related to the heart. The most common symptoms include fatigue, dyspnea on exertion, arrhythmias (both supraventricular and ventricular), palpitations and chest pain at rest. Many cases of myocarditis present with de novo onset of heart failure, with or without chest discomfort. When other causes of the heart failure syndrome are not evident following routine diagnostic assessment, viral myocarditis, along with idiopathic dilated cardiomyopathy, becomes the diagnosis of exclusion. Importantly, a history of exposure to cardiac toxins, a family history of nonischemic heart failure and epicardial coronary disease must be excluded. Cardiac catheterization with coronary angiography may be required.

How do I diagnose it?

To date, no prospective validation of clinical criteria has been published, although proposed diagnostic criteria have been published on two occasions. The diagnosis of myocarditis is made in the setting of compatible clinical findings, when other etiologies of cardiac dysfunction have been ruled out. Biomarkers, including markers of myocyte necrosis (creatine kinase MB and troponin) and increased cardiac wall stress (BNP, NT-proBNP) are supportive of, but not definitive for the diagnosis of myocarditis. The ECG findings may include arrhythmias (ventricular or supraventricular), atrioventricular block, pattern of acute injury or pericarditis, nonspecific repolarization abnormalities or, rarely, may be normal. Echocardiographic findings may include segmental or global LV dysfunction, RV dysfunction or pericardial effusion.

Presently, EMB still provides the most specific diagnosis for myocarditis. The Dallas criteria require an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event (59). Borderline myocarditis requires a less intense inflammatory infiltrate and no light microscopic evidence of myocyte destruction. There are many limitations associated with the Dallas criteria, and its value as a singular diagnostic tool has been questioned (60). Sensitivity is also limited due to sampling error related to the potentially focal nature of the myocardial inflammation. Guidance of EMB by CMR is currently under investigation. As such, clinicians are frequently reluctant to perform EMB due to the lack of sensitivity of a biopsy-based diagnosis, and the low likelihood (less than 5%) that the findings would lead to a change in therapy. Despite this, EMB remains the gold standard for making an unequivocal diagnosis. Recently, the International Consensus Group on Cardiavascular MR in Myocarditis (61) proposed diagnostic CMR criteria (the Lake Louise Consensus Criteria) for myocarditis, which may enhance the ability to detect myocardial inflammation through noninvasive CMR, as well as to improve diagnostic accuracy. In these criteria, four major domains are considered when making the diagnosis: clinical presentation compatible with myocarditis, evidence of new or recent onset myocardial damage, increased T2 signal or delayed enhancement on CMR (compatible with myocardial edema and inflammation), and EMB evidence of myocardial inflammation.

How should I treat it?

Patients with known or suspected myocarditis should be referred to a centre where expertise in the diagnostic assessment and treatment of myocarditis is available. The urgency of referral is dependent on the clinical course; those presenting with cardiogenic shock should be transferred immediately. A small proportion of patients will present with fulminant heart failure and require support ranging from positive inotropic agents and/or vasopressors, to mechanical circulatory support. Irrespective of clinical presentation, patients with myocarditis and heart failure should be treated with typical measures (for example, angiotensin-converting enzyme inhibitors, beta-blockers and diuretics if necessary) (1).

Immunosuppression is not routinely recommended for patients with myocarditis. However, patients with giant cell myocarditis, myocarditis due to autoimmune or hypersensitivity reactions, or patients with severe hemodynamic compromise and deteriorating conditions may benefit from a trial of immunosuppressive therapy. Investigational therapies, such as interferon, intravenous immune globulin, and other specific therapies for myocarditis are currently under evaluation and are not currently recommended for routine use.

When do I refer the patient?

Patients with suspected or known myocarditis should be referred to a centre with experience and expertise in the diagnosis and management of this condition. The prognosis for patients with myocarditis is usually favourable. One prospective study suggested that approximately one-third of patients presenting with acute myocarditis do not develop heart failure, one-third develop ventricular dysfunction with subsequent recovery, and approximately one-third are left with significant ventricular dysfunction – a small subgroup of whom progressively deteriorate and require significant support (mechanical circulatory support or cardiac transplantation) (62,63). Patients with evidence of progressive deterioration and evidence of significant end-organ damage related to poor perfusion should be referred to a heart transplantation centre for consideration of transplantation or mechanical circulatory support. Patients who fail to recover on standard heart failure therapy should also be referred for further evaluation and consideration of transplantation or mechanical circulatory support. Reports of small case series suggest that aggressive medical support, including a ventricular assist device, along with medical therapy, has allowed for eventual ventricular recovery and device explantation (64,65).

When do I follow up?

The intensity of follow-up for patients with myocarditis is dictated by the extent of cardiac dysfunction, the severity of the clinical presentation and the response to therapy. Follow-up consists of ongoing clinical assessment and may include echocardiographic assessment of cardiac function or CMR evaluation of ongoing inflammation. Emerging evidence suggests that CMR follow-up may be useful for predicting outcomes (66). Persistent inflammation at four weeks follow-up indicates a worse prognosis in patients with no further inflammation. Patients demonstrating a positive clinical response to therapy, including improvement in or normalization of cardiac dysfunction, should also undergo clinical follow-up within approximately three to six months to confirm clinical stability. Patients demonstrating a continued or worsening course, which will be dictated by the clinical severity of symptoms and LV dysfunction, require ongoing expert follow-up. These patients should be managed according to the standard heart failure recommendations (1).

DEVICE THERAPY FOR HEART FAILURE

ICD

Recommendations

- The decision to implant a device in a heart failure patient should be made with assessment and discussion between the heart failure and arrhythmia specialists (class I, level C).
- Referral for ICD therapy should be considered for patients with ischemic heart disease with or without mild to moderate heart failure symptoms and an LV ejection fraction of less than or equal to 30%, measured at least one month after myocardial infarction and at least three months following the coronary revascularization procedure (class I, level A).
- An ICD may be considered in patients with nonischemic cardiomyopathy present for at least nine months, New York Heart Association (NYHA) functional class II to III heart failure, and an LV ejection fraction of less than or equal to 30% (class IIa, level B) or an LV ejection fraction of 31% to 35% (class IIb, level C).
- An ICD may be considered in patients with ischemic heart disease, previous myocardial infarction, LV dysfunction (LV ejection fraction of 31% to 35%) measured at least one month after myocardial infarction and three months after coronary revascularization and with inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study (class IIa, level B), or with either no inducible ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study or without an electrophysiology study (class IIb, level C).
- An ICD should not be implanted in patients with poor life expectancy due to noncardiac disease or NYHA class IV heart failure who are not expected to improve with further therapy and who are not candidates for cardiac transplantation (class III, level C).
- Antiarrhythmic drug therapy is discouraged in heart failure patients unless symptomatic arrhythmias persist despite optimal medical therapy with angiotensin-converting enzyme (ACE) inhibitor plus beta-blocker, and correction of any ischemia or electrolyte and metabolic abnormalities (class I, level B).

Practical tips

- The decision to implant an ICD in any given patient should be individualized because subgroup analyses of clinical trials have suggested that some patients may not benefit from an ICD.
- Patients with significant comorbidities may not benefit from an ICD. Resynchronization may be an option in this population to improve quality of life.
- Subgroup analyses of primary prevention trials have suggested that the relative and absolute benefits in patients with an LV ejection fraction of between 31% and 35% may be smaller. An electrophysiological study may help to select higher-risk patients in this group.
- Cardiac resynchronization therapy (CRT) and ICD (CRT/ICD) in highly selected patients with heart failure believed to be 'end stage' may, in some cases, be considered on the grounds that CRT/ICD may, in itself, improve their prognosis.
- Patients being considered for ICD should have a reasonable quality of life and a life expectancy of greater than one year.

Since the 2006 CCS heart failure guidelines update, no new indications for ICD therapy have arisen and the reader is referred to that document (1). Results from systematic reviews of observational and randomized ICD trials confirm the favourable risk-benefit ratio of this therapy (67). One such review, based on 12 randomized trials (8516 patients) and 76 observational studies (96,951 patients), showed perspective ICD effectiveness. In this review, ICD therapy was associated with a 20% reduction in all-cause mortality. This was achieved with a 1.2% implant mortality and a total 3.5% annual likelihood of complications such as device malfunctions, lead problems or infections. There was a 4% to 20% range of annual inappropriate discharge rates. We continue to emphasize that, in addition to cardiac status, consideration of other comorbid conditions, patient desires and goals of therapy are essential components in the assessment for prescription of ICD therapy in this group of patients. In addition, close collaboration between the referring or heart failure physician and the arrhythmia specialist is essential, not only in the initial assessment of these patients, but in their follow-up. As noted below, the inclusion of invasive hemodynamic monitoring as a component of ICD implantation will mandate clear delineation of physician responsibilities in terms of responsibility and communication of monitoring results. A recent joint Heart Rhythm Society/European Heart Rhythm Association statement has outlined important considerations for these interactions (68).

Cardiac resynchronization therapy

Recommendations

- Patients with symptomatic (NYHA class III or IV) heart failure despite optimal medical therapy, who are in normal sinus rhythm with a QRS duration longer than 120 ms and an LV ejection fraction of less than 35%, should be considered for CRT (class I, level A).
- Routine CRT implantation is not currently recommended for patients with heart failure and a narrow QRS (less than 120 ms), either with or without concurrent ICD implantation (class III, level B).

Practical tips

- Patients with heart failure and an LV ejection fraction of less than 35%, and who are under consideration for ICD therapy should also undergo assessment for CRT therapy and vice versa (ie, considered for a combined ICD-CRT device).
- Patients enrolled in CRT studies who show benefit have a QRS duration averaging more than 150 ms. Therefore, it is unclear to what degree patients with an intermediate QRS duration (120 ms to 150 ms) will benefit from this therapy; because many randomized studies showing CRT benefit have included patients with a QRS duration longer than 130 ms, the benefit in patients with a QRS duration of 120 ms to 130 ms is even less well understood.
- Echocardiography-derived parameters of dyssynchrony are often used to help identify patients who may benefit from CRT but cannot be recommended on a routine basis, since clinical utility for the prediction of clinical response to CRT has not been established.
- In highly selected patients with refractory NYHA class III or IV heart failure, an LV ejection fraction of 35% or less, a QRS duration of 150 ms or more, and atrial fibrillation with controlled heart rate on optimal medial therapy, CRT may be a reasonable option.
- The use of CRT may prevent or reduce worsening LV systolic function in patients with LV systolic dysfunction who are receiving optimal recommended medical therapy, who require permanent ventricular pacing and who are expected to pace the majority of the time.
- Although studies are ongoing, no reliable method of dyssynchrony measurement predictive of clinical response to CRT has been identified to date.

Despite patient education, lifestyle modification and improved pharmacological therapy available for heart failure, many patients have persistent severe symptoms. Commonly, these patients have intra- and interventricular conduction delays that are associated with cardiac mechanical dyssynchrony. Several landmark studies have demonstrated the effectiveness of CRT to improve morbidity and mortality in selected patients with systolic heart failure. A recently published

systematic review (69) (including 14 randomized trials and more than 4400 patients, as well as 89 safety studies including more than 9677 patients) suggested that for CRT eligible patients, the procedural success rate was 93%, with a 0.3% procedural mortality. There could be an expectation of a 3% increase in LV ejection fraction, a 59% likelihood of improvement of one NYHA class, a 33% and 22% reduction in hospitalization and mortality, respectively and approximately a 10% one-year chance of device or lead malfunction. Since 2006, we revisit the Cardiac Resynchronization in Heart Failure (CARE-HF) studies and outline two others.

The CARE-HF (70) study enrolled 813 patients with NYHA class III or IV symptoms, an LV end-diastolic dimension of 30 mm or more (indexed to height), an LV ejection fraction of 35% or less and a prolonged QRS (120 ms or longer). In addition, evidence of mechanical dyssynchrony was necessary for patients with a QRS of 120 ms to 149 ms, by echocardiography criteria (two of the following three: an aortic pre-ejection delay of more than 140 ms; an interventricular mechanical delay of more than 40 ms; or delayed activation of the posterolateral LV wall). The primary end point (time to death from any cause or an unplanned hospitalization for a major cardiovascular event) was significantly decreased in the CRT group compared with the medical therapy group (hazard ratio [HR] 0.63, 95% CI 0.51 to 0.77; P<0.001). Compared with medical therapy, CRT reduced the interventricular mechanical delay, the end-systolic volume index and the area of the mitral regurgitant jet, increased the LV ejection fraction, and improved symptoms and quality of life (P<0.01 for all comparisons).

A prospective, nonrandomized multicentre study, the Predictors of Response to CRT (PROSPECT) (71) trial, tested the performance of 12 echocardiographic parameters of dyssynchrony, based on both conventional and tissue Doppler-based methods to predict CRT response at six months. The study enrolled 498 patients on a stable medical regimen with standard CRT indications (NYHA class III or IV symptoms, LV ejection fraction of 35% or less, QRS interval of 130 ms or longer). The sensitivity and specificity of these echocardiographic parameters to predict the clinical and remodelling composite outcomes varied widely, ranging from 6% to 74% for sensitivity and from 35% to 91% for specificity, with large variability in the analysis of the dyssynchrony parameters. Results of this study suggest that no single echocardiographic measurement of mechanical dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines.

The benefit of CRT in patients with wide QRS is well established. However, some patients with narrow QRS complexes have echocardiographic evidence of LV mechanical dyssynchrony and may also benefit from CRT. The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) (72) trial enrolled 172 patients who had a standard indication for an ICD, LV ejection fraction of less than 35%, moderate symptoms of heart failure (NYHA class III) caused by either ischemic or nonischemic cardiomyopathy, and a QRS interval of less than 130 ms. Patients received the CRT device and were randomly assigned to the CRT group or to a control group (no CRT) for six months. There was no change in the primary end point (peak oxygen consumption during cardiopulmonary exercise testing at six months), or change in quality-of-life scores, 6 min walking test results or ejection fraction.

The use of CRT in patients with LV systolic dysfunction who require permanent ventricular pacing, or in patients with suspected RV pacing-induced heart failure has been investigated in small trials (73,74). The results of these studies suggest that the use of CRT in this clinical situation improves LV function, symptoms and exercise capacity. However, this potential indication has not been properly evaluated in a prospective clinical trial.

Unanswered questions remain about exactly who benefits from CRT therapy. Why do all severely symptomatic patients with a wide QRS not benefit from this form of therapy? Does the QRS duration itself matter as much as the finding of cardiac dyssynchrony on echocardiography? What is the best way to evaluate cardiac dyssynchrony? What is the role of CRT in patients with chronic atrial fibrillation? Should CRT be used in less symptomatic patients to prevent the progression of symptoms? Is there a better way to optimize CRT function by using certain echocardiographic parameters? Several smaller studies have attempted to answer these questions, but the results are not conclusive.

Invasive hemodynamic monitoring

Recommendation

- The use of routine pulmonary artery catheterization for the treatment of patients hospitalized with severe symptomatic and recurrent heart failure in addition to careful clinical assessment is not recommended (class III, level B).

Practical tips

- There is not enough clinical data to support routine implantation of a continuous hemodynamic monitor to guide patient management in addition to optimal medical therapy. Further data will become available in ongoing trials.
- Tailored hemodynamic therapy with a pulmonary artery catheter under experienced supervision may be clinically useful in highly selected cases, such as ongoing heart failure accompanied by cardiorenal syndrome, poor response to therapy or systemic hypotension.

Implantable hemodynamic monitor

Patients with impending decompensation of heart failure can demonstrate an increase in pulmonary and cardiac filling pressures many days or even weeks before the clinical deterioration. Because it is difficult to clinically predict heart failure decompensation, efforts to develop an early warning system (and theoretically allow for early, preventive intervention) in high-risk patients are ongoing. One method, direct measurement of intracardiac pressures via an indwelling lead, is now under investigation. The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) (75) study was a prospective, multicentre, randomized, single-blind, parallel-controlled trial evaluating the use of an implantable continuous hemodynamic monitor (attached to a pacemaker-like lead and situated in the RV outflow tract) in 274 patients with advanced heart failure. Patients were randomly assigned to optimal medical therapy or hemodynamic-guided therapy, which consisted of optimal medical therapy plus the results of weekly downloading of patient hemodynamic data. All patients underwent device implantation, but the hemodynamic information from the monitor was used to guide patient management only in the last group.

There were two primary end points, including safety (freedom from system-related complications, freedom from pressure-sensor failure) and efficacy (reduction in heart failure-related events such as hospitalizations and emergency department consultations). There were no pressure-sensor failures, and system-related complications occurred in 8% of the patients, without any benefit in all heart failure-related events (a non-significant 21% reduction was observed in the Chronicle group compared with controls; P=0.33). Interestingly, a retrospective analysis of the time to first hospitalization for heart failure showed a 36% reduction (P=0.03) in the RR of a heart failure-related hospitalization in the intervention group. Additional trials are needed to establish the potential clinical benefit of implantable continuous hemodynamic monitor-guided care in patients with advanced heart failure.

Monitoring of intrathoracic fluid accumulation

Newer-generation ICDs include the measurement of intrathoracic impedance, which varies inversely with the amount of intrathoracic fluid content. Through the application of proprietary algorithms (such as OptiVol [Medtronic Corporation, USA]), information can be downloaded from the ICD to allow estimation of intrathoracic fluid content and, therefore, may predict clinical decompensation. Small pilot studies have shown the feasibility of this approach, although data

from randomized trials with outcome assessments are not currently available.

Pulmonary artery catheter monitoring for patients hospitalized with advanced heart failure

Patients with heart failure and elevated filling pressures have increased morbidity and mortality. Unfortunately, clinical assessment alone in these patients is often inadequate when estimating cardiac filling pressures. Earlier studies have suggested that in hospitalized heart failure patients, institution of tailored hemodynamic therapy with combination vasodilator and diuretic, guided by intracardiac pressure measurement by right heart catheterization, is associated with improved functional capacity, symptoms and possibly outcomes. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) (76) study was a multicentre, randomized controlled trial that was stopped early after 433 patients (of the 500 originally planned) were enrolled, due to concerns of early adverse events and the unlikelihood of achieving a significant difference in the primary end point. The objectives of the trial were to determine whether tailored hemodynamic therapy with the use of pulmonary artery catheters (PACs) to guide therapy is safe and improves clinical outcomes in patients hospitalized with severe symptomatic and recurrent heart failure. Patients were randomly assigned to standard clinical management alone or PAC-guided therapy in addition to clinical assessment with targets of a pulmonary capillary wedge pressure of 15 mmHg or less, and an RA pressure of 8 mmHg or less.

Therapy in both groups led to a substantial reduction in symptoms, jugular venous pressure and edema. Use of the PAC did not significantly affect the primary end point of days alive and out of the hospital during the first six months (133 days versus 135 days; HR 1.00, 95% CI 0.82 to 1.21; P=0.99), mortality (43 patients [10%] versus 38 patients [9%]; OR 1.26, 95% CI 0.78 to 2.03; P=0.35), or the number of days hospitalized (8.7 days versus 8.3 days; HR 1.04, 95% CI 0.86 to 1.27; P=0.67). In-hospital adverse events were more common among patients in the PAC group (n=47 [21.9%] versus n=25 [11.5%]; P=0.04). Exercise and quality of life end points improved in both groups, with a trend toward greater improvement with PACs, which reached significance for the time trade-off at all time points after random assignment.

LANDMARK CLINICAL TRIALS CHANGING STANDARD CARE

Prevention of heart failure

Recommendations

- Elderly patients older than 80 years of age, with sustained sitting BP greater than 160/90 mmHg and standing systolic BP higher than 140 mmHg, should be considered for BP lowering to 150/80 mmHg to reduce their risk of developing new heart failure depending on comorbidities and patient preference (class I, level A).
- An ACE inhibitor or angiotensin receptor blocker (ARB) should be prescribed in known effective doses to reduce the risk of developing HF in patients with evidence of vascular disease or diabetes with end-organ damage (class I, level A).
- In ACE-intolerant patients, an ARB may be considered for reduction of the risk of developing HF in patients with evidence of vascular disease or diabetes with end-organ damage (class IIa, level B).

Practical tips

- BP goal is less than 140/90 mmHg in most individuals and less than 130/80 mmHg in patients with diabetes and/or chronic kidney disease.
- In high-risk patients with multiple risk factors for HF, it may be useful to reduce BP even if it is within the normal range.
- Caution should be exercised in the administration of antihypertensive agents in elderly patients, especially in those who are frail or who exhibit symptoms or a clinically significant postural drop (more than 20 mmHg) in BP. This patient population is at increased risk for side effects of therapy and has been excluded from hypertension studies showing clinical benefits of antihypertensive treatment.
- While thiazolidinedione (TZD) therapy may be appropriate for highly selected individuals with diabetes and stable HF, the use of TZD therapy is associated with increased incidence of HF in patients at risk for this condition.
- The choice of an ACE inhibitor or ARB to prevent or treat HF should be based on drugs and doses shown to be effective in adequately designed and conducted clinical trials.

Despite state-of-the-art therapy, including the implantable defibrillator, five-year mortality of patients with stable heart failure due to reduced systolic LV function and no other major illnesses is still approximately 30% (77). To date, no therapy has been shown to improve mortality in patients with heart failure and preserved LV ejection fraction (or diastolic heart failure), or in those with acutely decompensated heart failure. As previously mentioned in the 2007 update, in which prevention of heart failure was discussed, improved treatment of patients with both acute and chronic vascular conditions, such as acute myocardial infarction, together with increased population age demographics, prevalence of diabetes and obesity, will contribute to an enlarging pool of patients at risk for heart failure. The result is the increasing importance of heart failure prevention (2).

In 2009, we update this information with results from several landmark studies. Elderly patients are at highest risk for developing heart failure. However, until 2008, evidence that treatment of the very elderly (older than 80 years of age) will improve morbidity and mortality (including new-onset heart failure) was lacking. Indeed, a previous meta-analysis (78) suggested that the treatment of very elderly individuals with hypertension would reduce stroke but at the cost of increased cardiac events. In the Hypertension in the Very Elderly Trial (HYVET) (79), elderly patients (older than 80 years of age) with sustained hypertension (defined as systolic BP higher than 160 mmHg) were randomly assigned to a diuretic with or without ACE inhibitor regimen, or placebo. This study was prematurely terminated due to an overwhelming reduction of the primary end point of fatal or nonfatal stroke in the active therapy group. In addition, other outcomes, including total mortality, cardiovascular mortality and new-onset heart failure, were reduced (HR 0.36, 95% CI 0.22 to 0.58; P<0.001), based on 79 events), nearly 65% with treatment of elevated BP. Results from HYVET extend the known benefits of antihypertensive therapy to the very elderly. However, despite these findings, clinicians are again cautioned that treatment of hypertension in very elderly patients must be balanced against the increased risk of the side effects associated with therapy, particularly in those who are frail or have an increased comorbid illness burden.

In the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study (80), 25,620 patients 55 years of age or older with established vascular disease, or with diabetes and end organ damage, were randomly assigned to receive ramipril 10 mg daily, telmisartan 80 mg daily or a combination of both drugs. The primary end point was a composite of mortality, nonfatal myocardial infarction, nonfatal stroke or hospitalization for new-onset heart failure and patients were followed for a median of 56 months in this study, which was powered for superiority of the combination over either drug alone, as well as for noninferiority of telmisartan to ramipril. There was no difference in the primary outcome or in the heart failure component. While telmisartan did meet the a priori threshold for noninferiority to ramipril, there was no additional benefit with the combination. The results of this trial suggested that ramipril 10 mg and telmisartan 80 mg may be used with similar expectations for benefits in this patient population.

The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial (81) was published in the fall of 2008. In this trial, 5926 patients were randomly assigned to either telmisartan 80 mg or to placebo. This study was designed to show the superiority of telmisartan and enforced enrolment criteria similar to the ONTARGET study, with the additional requirement that patients must have been documented to be intolerant to ACE inhibitors. Approximately 75% of the patients had hypertension, 75% had coronary artery disease, 22% had a history of stroke or transient ischemic attack, and 36% had diabetes. By the end of the study, a small proportion of the patients were on ARBs other than telmisartan (7%). The primary end point of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure was similar between the ARB and placebo arms (HR 0.92, 95% CI 0.81 to 1.05). Surprisingly, and despite a reduction in mean BP (3.2/1.3 mmHg, P<0.0001) and less new-onset LV hypertrophy (5.0% versus 7.9%, P<0.0001), no difference in hospitalization for heart failure (4.5% versus 4.3%, P=0.69) was seen with telmisartan. Potential explanations underlying the results of TRANSCEND (given their apparent conflict with ONTARGET) include the possible increased use of diuretics in the placebo arm, the low rate of heart failure seen (less than 0.9% annual incidence), the very small difference in mean BP in a population with controlled BP, the particular features of the study population (ie, ACE-intolerant) or by chance. Previous studies of ARB therapy in high-risk vascular patients (ie, diabetic nephropathy, postmyocardial infarction, high-risk hypertension) have shown more benefits than placebo and similarity to ACE inhibitors.

In the Jikei Heart Study (82), 3081 Japanese controlled hypertensive patients were randomly assigned, in an open-label fashion, to further BP reduction to a goal of 130/80 mmHg using either the ARB valsartan, or to any regimen that did not include an ACE inhibitor or ARB (although more than one-third of patients did receive these). The primary end point was a composite of several vascular events including doubling of serum creatinine levels, transition to renal replacement therapy, and hospitalization for heart failure, stroke, myocardial infarction, unstable angina, aortic dissection or cardiovascular mortality. Systemic BP in this trial was reduced from 139/81 mmHg to 132/78 mmHg with no difference in either the valsartan or placebo group. The study required early termination, on the advice of the data safety committee, due to a large reduction in the primary composite end point. In this trial, hospitalization due to heart failure was reduced by 46% (HR 0.54, 95% CI 0.31to 0.94; P=0.029). This result was based on only 55 events (36 versus 19 events) and was not accompanied by a decrease in nonfatal myocardial infarction or cardiovascular mortality. The open-label design of the trial, in the context of subjective end point inclusion, lack of consistent end point reduction and use of a highly selected population, limit the generalizability of the findings.

Therefore, either ACE inhibitors or ARBs are acceptable therapies for the prevention of heart failure in patients older than 55 years of age with known vascular disease or with diabetes and other risk factors. Additionally, and while conflicting evidence exists, the balance of evidence supports ARB therapy for the prevention of new-onset heart failure in ACE-intolerant patients with known vascular disease or diabetes and additional risk factors.

Control of blood glucose levels according to existing Canadian Diabetes Association recommendations are affirmed, although optimal glucose-lowering regimens for type 2 diabetes are not explicitly stated. In recent years, TZDs have been advocated as effective antidiabetic medications. Despite their known fluid retention effects, TZDs do not appear to directly affect cardiac function. Previous CCS heart failure updates have allowed for their use in stable patients, provided their heart failure was controlled and heightened awareness for clinical decompensation was exercised (83,84). As noted in the 2007 update, the large PROspective pioglitAzone (PROactive) study (85) documented a small but significant excess (0.7% annual increase) of new-onset heart failure with the use of pioglitazone versus placebo. Further evidence has accumulated through randomized clinical trials, as well as through registry-based data, that the use of TZDs, especially rosiglitazone, for control of blood glucose, is associated with increased incidence of heart failure, placing this class of drug in the list of those that may precipitate or cause heart failure (86,87). As such, if a suitable alternative exists, avoidance of these medications may be preferred.

Treatment of heart failure (treatment of anemia in heart failure)

Recommendations

- Patients with heart failure and anemia (plasma hemoglobin lower than 110 g/L or hematocrit less than 35%) should be carefully evaluated for underlying causes such as chronic blood loss or other inflammatory illness. Iron, vitamin B_{12} or folate deficiency should be corrected as appropriate (class I, level B).

Anemia is a relatively common comorbidity among heart failure patients, in whom it may aggravate heart failure symptoms and has been associated with increased morbidity and mortality. The role of iron supplementation and bone marrow-stimulating therapies in anemic heart failure patients was recently examined in two clinical trials. A randomized, double-blind, controlled, multicentre trial (88) enrolled 319 patients with NYHA class I or III heart failure, LV ejection fraction of less than 40%, hemoglobin 90 g/L to 120 g/L, and a baseline treadmill capacity of at least 2 min were randomly assigned to darbepoetin alfa or placebo twice per month. After 52 weeks, despite statistically significant improvements in hemoglobin, the intervention group experienced no improvement in the primary end point of exercise duration, functional class or symptoms, and a non-significant trend toward lower all-cause mortality and first heart failure hospitalization. In a second double-blind, randomized controlled single-centre trial of 51 patients with NYHA III or IV functional class, LV ejection fraction of less than 40%, creatinine clearance of 30 mL/min to 60 mL/min, and baseline hemoglobin of 115 g/L, the effect of twice weekly erythropoietin injections was compared with placebo injections (89). All patients received iron therapy. After 12 months, intervention patients experienced statistically significant improvements in hemoglobin, measures of ventricular function and functional class, and fewer hospitalizations. Randomized trials have examined the effect of intravenous iron supplementation in patients with documented iron deficiency, mild anemia, heart failure and LV ejection fraction of less than 40%. Results of short-term studies (90,91) indicate an improvement in LV size and function, improved symptoms and exercise tolerance. These trials support further work in studies of anemia and heart failure, and provide support for iron supplementation in iron-deficient heart failure patients with anemia and for continuation of the ongoing Reduction of events with Darbepoetin alfa in Heart Failure (RED-HF) (92) study and the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (93).

Omega-3 polyunsaturated fatty acid (or fish oil) supplementation

Recommendation

- Low-dose omega-3 polyunsaturated fatty acid (n-3 PUFA) therapy (1 g/day) may be considered for reduction in morbidity and mortality in patients with mild-to-moderate heart failure (class 2a, level B).

Practical tips

- Most of the data available for n-3 PUFAs have been reported in patients with heart failure and an ejection fraction of less than 40%. Consequently, extrapolation of these results to patients with heart failure and preserved ejection fraction should be made with caution.
- With most data, the dose of n-3 PUFA is 1 g/day. It is unknown whether higher or lower doses would confer clinical benefit and they are therefore not suggested. Doses greater than 3 g/day are associated with excessive bleeding.

- n-3 PUFA therapy may affect measures of anticoagulation. Close monitoring of the international normalized ratio in patients taking warfarin following institution of n-3 PUFA is suggested.
- According to manufacturers, there is evidence of significant variability in the content of n-3 PUFA. Patients considering n-3 PUFA should consult with their pharmacist to select a reliable supplement brand that most closely matches formulations shown to be effective in clinical trials.

n-3 PUFAs are known to have beneficial effects on lipid levels, and studies suggest a possible direct effect on the myocardium. Data from mechanistic studies of failing hearts show that particularly high n-3 PUFA levels are associated with a shift from reliance on myocardial fatty acid as a primary energy source toward more normal reliance on glucose. These findings were associated with fewer measured markers of myocardial oxidative stress and inflammation, improved plasma membrane stability and myocardial energy efficiency (94-96). The lipid, but not myocardial effects, have been shown with eicosapentanoids such as vegetable oils (95,97). This has led to speculation that n-3 PUFA would reduce the occurrence of cardiac disease, or sudden or even total cardiac death (98-100). Results of earlier studies, which generally evaluated moderate or higher doses of n-3 PUFA, were inconsistent (101,102). Nevertheless, the data on balance have favoured a modest beneficial effect on adverse outcomes in the range of approximately 10%. The Gruppo Italiano per lo Studio della Sopravvivenza nell-Infarto Miocardico (GISSI)-Prevenzione trial (103) supported a reduction of SCD, but not total mortality in patients with existing cardiac disease.

The GISSI-HF study was a large trial designed to assess the effects of n-3 PUFAs and rosuvastatin in symptomatic heart failure (104). This was a 2×2 randomization in which 7000 patients with symptomatic NYHA functional class II to IV heart failure, irrespective of etiology or ejection fraction, were first randomly assigned to a relatively low dose of fish-based n-3 PUFA (daily 850 mg to 882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1•2) or placebo. Participants with no clear indication or contraindication to cholesterol-lowering therapy were further randomly assigned (n=4574) to low-dose rosuvastatin 10 mg or placebo. The primary end points were time to death, and time to death or admission to hospital for cardiovascular reasons. After a median 3.9 years follow-up in this otherwise well-treated cohort, patients treated with n-3 PUFA experienced a modest yet statistically significant 10% relative reduction in cardiovascular events compared with the placebo arm. Death and hospitalization were affected equally. No statistically significant reduction in sudden cardiac death was seen. The therapy was well tolerated with primarily gastrointestinal side effects, and fewer than 10% of patients required study drug withdrawal. These results confirm a modest benefit from n-3 PUFA in patients with heart failure, with an unclear predominance of effect in any particular subgroup. It is unknown whether a higher dose of drug would have provided a similar or greater benefit and the precise mechanism of action is unclear (105). In addition, current sources of n-3 PUFA are considered to be food supplements and, therefore, are not subject to the intense regulatory scrutiny (including predefined tolerances for drug content) that is required for any drug approval. The result is that it is difficult to be certain of the amount of n-3 PUFA present in any given commercial preparation. Indeed, evidence suggests a large degree of variability between different available forms of n-3 PUFA (106). Patients and caregivers who wish to use n-3 PUFA are therefore referred to a local hospital, pharmacy or other reputable source of information to determine their best source of n-3 PUFA. Reports of excessive bleeding have been associated with doses higher than 3 g/day (107).

3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins)

Recommendation

- Statin therapy may be considered for patients with systolic heart failure of ischemic etiology in accordance with primary and secondary prevention guidelines (class 2A, level B).

Practical tips

- Routine statin therapy is unlikely to provide clinical benefit for patients with active heart failure due to nonischemic causes and in the absence of very high risk of vascular events (such as recent myocardial infarction, diabetes and known vascular disease).
- Current data are insufficient to provide strong recommendations regarding statin therapy and diastolic heart failure, so the decision to treat should be made on the basis of existing prevention guidelines.
- It is reasonable to consider statin withdrawal in patients with refractory heart failure, or where reduction in polypharmacy or palliative care is an overriding concern.

Many patients with heart failure have coexistent ischemic heart disease. This fact, coupled with evidence that control of vascular risk factors such as hypertension and dyslipidemia reduces progression to heart failure, has led to speculation that treatment of elevated low-density lipoprotein cholesterol with statin therapy may reduce death and/or progression of heart failure (108). Retrospective and nonrandomized observational studies have suggested an impressive mortality reduction in heart failure patients treated with statins (109). However, until recently, definitive randomized studies of statin therapy in heart failure patients were lacking (110).

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study was a randomized, parallel, double-blind, placebo-controlled study of 5011 stable heart failure patients (111). They were required to be 60 years of age or older (mean [± SD] age 73±7 years), have heart failure presumed to be of ischemic origin, LV ejection fraction of less than 40%, and NYHA functional class of II to IV. Patients were followed for just under three years. Patients randomly assigned to receive rosuvastatin experienced a nonsignificant 8% reduction in the risk of a primary end point of cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke. Rosuvastatin was associated with a significant reduction in all-cause hospitalizations (3694 in the rosuvastatin arm versus 4074 in the placebo arm, P=0.007). This finding was driven by less cardiovascular hospitalization, including for acutely decompensated heart failure, as well as in fatal or nonfatal myocardial infarction or stroke. Rosuvastatin was well tolerated, with fewer withdrawals from therapy than with placebo.

In the GISSI-HF study, 4574 patients 18 years of age or older with chronic heart failure of NYHA class II to IV, irrespective of cause and LV ejection fraction, were randomly assigned to rosuvastatin 10 mg daily or placebo, and followed for a median of nearly four years (112). Primary end points were time to death, and time to death or admission to hospital for cardiovascular reasons. In the rosuvastatin group, 657 (29%) patients died from any cause versus 644 (28%) in the placebo group. There were 1305 (57%) patients in the rosuvastatin group and 1283 (56%) in the placebo group who died or were admitted to hospital for a cardiovascular reason.

These two landmark trials show elements of concordance as well as differences. Neither study showed any effect on mortality. However, the CORONA study showed a reduction in hospitalization while the GISSI-HF study did not. The different results are not due to the intervention, which was identical in both studies, but more likely reflect differences in patient populations. Compared with those in GISSI-HF, patients enrolled in the CORONA trial were older, and more likely to have LV systolic dysfunction and in NYHA functional class III. While all patients enrolled in CORONA had heart failure due to ischemic heart disease, fewer than 40% of those in GISSI-HF were of ischemic etiology. In addition, participants in GISSI-HF could have not had a clear indication for or against statin therapy, which may have led investigators to select patients at lower atherosclerotic risk for further randomization in the statin portion of that study. Therefore, patients enrolled in CORONA had a higher baseline cardiovascular risk and, therefore, a higher expected event rate for total hospitalization and vascular events. It is important to recognize that these were trials of statin addition, rather than statin withdrawal, and as such, do not

provide specific guidance as to when statin therapy should be stopped. However, studies addressing this question are unlikely to be performed.

Rhythm versus rate control of atrial fibrillation in heart failure

Recommendation

- In patients with stable heart failure and atrial fibrillation (AF), rate control is an acceptable management strategy and routine rhythm control is not required (class I, level B).

Practical tip

- In patients who are symptomatic from AF or whose symptoms of heart failure are believed to have substantial contribution from arrhythmia, consideration can be given for rhythm control.

AF is prevalent in patients with heart failure (113,114), and the development of AF is associated with an increase in morbidity and mortality in these patients (115). A decision that physicians frequently have to make in patients with AF is whether to attempt to maintain sinus rhythm. Rate versus rhythm control trials in patients without heart failure have shown no additional benefit of the rhythm control strategy (116). However, patients with heart failure and AF were thought, by many clinicians, to be at higher risk and to potentially be in greater need of sinus rhythm than their counterparts without heart failure.

The Atrial Fibrillation in Congestive Heart Failure trial (AF-CHF) study was a prospective randomized controlled trial designed to determine whether restoring and maintaining sinus rhythm reduces cardiovascular mortality compared with a rate control strategy in patients with AF and stable systolic heart failure. Details of the rationale and methodology have been published previously (117). In this study, 1376 patients with NYHA class II to IV heart failure and LV ejection fraction of less than 35% (NYHA class I patients with prior hospitalization for heart failure or ejection fraction of less than 25% were also eligible) and a documented clinically significant episode of AF within the past six months were randomly assigned to one of two treatment strategies: rhythm control with the use of electrical cardioversion combined with antiarrhythmic drugs (amiodarone or other class III agents), and additional nonpharmacological therapy in resistant patients; and rate control with the use of beta-blockers, digoxin or pacemaker and atrioventricular node ablation if necessary.

The primary end point was cardiovascular mortality. At the end, 682 patients were randomly assigned to rhythm control and 694 to rate control. At baseline, AF was paroxysmal in 31% of patients and the mean ejection fraction was 27%. Importantly, investigators were encouraged to not randomize patients they believed clearly did not tolerate their arrhythmia and to attempt restoration of sinus rhythm. By trial design, rhythm control was predominantly achieved with amiodarone (82%) with less use of sotalol (1.8%) and dofetilide (0.4%) in the rhythm control cohort. In the rate control group, beta-blockers were used in 88% of patients and digoxin in 75%. Crossover from rhythm to rate control occurred in 21% of the rhythm group and from rate to rhythm control in 10% of the rate group. There was no difference in the primary end point between the groups (26.7% of the rhythm control group versus 25.2% of the rate control group; HR 1.06, 95% CI 0.86 to 1.30; P=0.59). There was also no difference in total mortality (31.8% versus 32.9%, P=0.73), stroke (2.6% versus 3.6%, P=0.32), worsening heart failure (27.6% versus 30.8%, P=0.17) or the composite of cardiovascular death, stroke or worsening heart failure (42.7% versus 45.8%, P=0.20) for rhythm control versus rate control, respectively. In the rhythm control group, 39% underwent electrical cardioversion compared with 8% of the rate control group (P=0.0001). Bradyarrhythmias were more common in the rhythm control group (8.5% versus 4.9%, P=0.007). Among patients with heart failure and AF, the use of rhythm control was not associated with differences in cardiovascular mortality compared with rate control through a mean follow-up of three years. These neutral results do not support the routine attempt to maintain sinus rhythm in heart failure if they are believed to be clinically stable while in AF. In addition, patients with atrial flutter were not enrolled in this trial and, as such, the results of the AF-CHF trial do not apply in that setting (1).

IMPORTANT CLINICAL TRIALS THAT DO NOT CHANGE CURRENT RECOMMENDATIONS

Natriuretic peptide-guided therapy with predefined target treatment values

The natriuretic peptides, namely BNP and the amino-terminal fragment of the prohormone, NT-proBNP, have evolved to be useful biomarkers of cardiac function as well as prognosis in heart failure. Large-scale studies have established a close association between the blood level of BNP and NT-proBNP, and the diagnosis of heart failure (118-122) and an independent prediction of mortality and heart failure events (123-127). Moreover, several randomized controlled trials have demonstrated that a treatment strategy that incorporates BNP or NT-proBNP measurement improves selected clinical outcomes and reduces treatment costs in patients presenting to the emergency department with acute dyspnea (122,128,129). Recommendations and practical tips for the use of BNP/NT-proBNP were provided in the 2007 update (2). One potential treatment strategy in patients with acute or chronic heart failure is a natriuretic peptide-guided approach, aiming for predefined target BNP or NT-proBNP values. An earlier pilot study by Troughton et al (130) was the first attempt to evaluate such an approach. In this study, 69 patients with decompensated heart failure were randomly assigned to have therapy according to a preset clinical algorithm, or according to NT-proBNP level. In the NT-proBNP-guided group, NT-proBNP levels above 200 pmol/L (approximately 1700 pg/mL) triggered intensification of therapy. At 9.5 months, clinical outcomes were significantly improved in the NT-proBNP-guided group.

The recently published Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) multicentre randomized trial was designed to evaluate the potential benefit of BNP-guided therapy on clinical outcomes in patients followed in heart failure clinics (131). These patients were recruited by heart failure specialists from 17 university hospitals. All investigators had expertise in heart failure management and were experienced in the interpretation of BNP results. A total of 220 patients with NYHA functional class II to III symptoms and LV ejection fraction of less than 45% considered optimally treated with ACE inhibitors, beta-blockers and diuretics were randomly assigned to medical treatment according to either current guidelines (clinical group) or a goal of decreasing plasma BNP to less than 100 pg/mL (BNP group). The primary combined end point was heart failure-related death or hospital stay for heart failure. During the first three months, all types of drugs were adjusted more frequently in the BNP group (specifically in pursuit of the BNP target on 80% of occasions). Mean dosages of ACE inhibitors and beta-blockers were higher in the BNP group, whereas the mean increase in diuretic dosage was similar in both groups. In a follow-up period of 15 months, there were fewer events – death or heart failure hospitalization – in the BNP group. There were no significant differences in all-cause mortality or all-cause hospitalization. The investigators therefore concluded that, in optimally treated patients with heart failure, a BNP-guided strategy with target blood BNP level reduced the risk of heart failure-related death or hospital stay for heart failure, and that the benefit was achieved mainly through an increase in ACE inhibitor and beta-blocker dosages.

These results, although very promising, warrant some caution in the interpretation for several reasons. First, the sample size of the trial was still relatively small. Second, the study was conducted in heart failure clinics where management was highly specialized and the clinicians were likely very familiar with the interpretation of BNP results. These results are therefore not applicable to heart failure patients who are not managed in specialized clinics by clinicians with expertise in the interpretation of serial BNP testing. The results of STARS-BNP

TABLE 6
Summary of recently completed randomized studies of therapies: Acutely decompensated heart failure

Study, sample size	Intervention	Results	Comments
SURVIVE (135), n=1327	Intravenous levosimendan versus dobutamine	No difference in 180-day total mortality (HR 0.91, 95% CI 0.74 to 1.13; P=0.40). No difference in dyspnea or other end point	Early improvement in short-term BNP levels in levosimendan group not translated to mortality. Levosimendan is not available in Canada
VERITAS (134), n=1448	24 h to 72 h of intravenous tezosentan	No difference in death or worsening heart failure at seven days (26.4% versus 26.3%, P=0.92). No difference in dyspnea score measured by visual analogue scale	Tezosentan is not available in Canada
EVEREST (136,137), n=4133	Oral tolvaptan versus placebo in 4133 patients	Improvement in primary composite end point of changes in global clinical status based on: visual analog scale and body weight at day seven or hospital discharge No improvement in dyspnea No difference in all-cause mortality (HR 0.98, 95% CI 0.87 to 1.11; P=0.68) or cardiovascular death or hospitalization for heart failure	Greater weight loss in tolvaptan arm. Tolvaptan not is available in Canada
UNLOAD (138), n=200	Venovenous ultrafiltration versus usual diuretic-based therapy in 200 patients	5.0±3.5 kg versus 3.1±3.5 kg; P=0.001. Weight loss at 48 h No difference in dyspnea score improvement	Secondary end point of 30-day repeat hospitalization reduced in intervention arm, although with few occurrences Significant increase in serum creatinine at all points of measurement

BNP B-type natriuretic peptide; EVEREST Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan trial; *HR Hazard ratio; SURVIVE* Levosimendan vs Dobutamine for patients With Acute Decompensated Heart Failure study; UNLOAD Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure stduy; VERITAS Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure study

therefore need to be verified by larger trials that incorporate a more general heart failure population and for the full range of available treatment options for heart failure.

The only remaining randomized controlled trial to be published that evaluated a BNP targeting approach is the New Zealand-based BNP-Assisted Treatment To LEssen Serial CARdiac REadmissions and Death (BATTLE-SCARRED) trial, which evaluated NT-proBNP-guided therapy with treatment based on predefined target NT-proBNP values (2). At this point, it is premature to incorporate the results of STARS-BNP and add the strategy of treating BNP/NT-proBNP to target values to the last updated consensus recommendations.

NONSPECIFIC IMMUNOMODULATION THERAPY FOR HEART FAILURE

Experimental evidence suggests that inflammatory mediators contribute to the progression of heart failure. Modulation of immune response therapy (IMT) therefore constitutes an attractive therapeutic strategy. In a pilot study of 73 patients with moderate heart failure, ex vivo exposure of autologous blood to oxidative stress followed by intramuscular injection suggested an improvement in clinical outcome (132). The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) study performed a double-blind, placebo-controlled comparison of a device-based IMT in patients with NYHA class II to IV heart failure, LV systolic dysfunction, and hospitalization for heart failure or intravenous drug therapy in an outpatient setting within the previous 12 months (133). Patients were randomly assigned to receive IMT (n=1213) or placebo (n=1213) by intragluteal injection. During a mean follow-up period of 10.2 months, there was no difference in the primary end point of time to death from any cause or any cardiovascular hospitalization (HR 0.92, 95% CI 0.80 to 1.05; P=0.22).

THERAPIES FOR ACUTELY DECOMPENSATED HEART FAILURE

Practical tip

- In highly selected cases of diuretic resistance and under experienced supervision, intermittent slow continuous veno-venous ultrafiltration may be considered.

Since acute decompensated heart failure was reviewed in the 2007 CCS heart failure guideline update, four large randomized trials in this area have been published: Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure (VERITAS) (134), SURVIVE (135), EVEREST (136,137) and the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study (138) (Table 6). In the VERITAS and SURVIVE trials, an intravenous dual endothelin antagonist and positive inotropic agent respectively, were evaluated and found not to meet their primary end points. In the EVEREST trial, tolvaptan, an oral inhibitor of antidiuretic hormone, was compared with placebo in patients with decompensated heart failure. Modest increments in weight loss and a complex composite clinical end point were seen during the initial in-hospital phase, while no long-term improvement in clinical outcomes was observed. Further details regarding these trials are shown in Table 6.

The vasodilator, nesiritide, is available in Canada by conditional approval, pending the results of the 7000-patient, international, randomized, placebo-controlled double-blind Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND), which will definitively show the effect of this medication on the morbidity and mortality of patients with this condition. This medication is an acceptable choice for treatment of warm and wet patients with acutely decompensated heart failure who have not responded to initial therapy and who are not eligible for enrolment in the ASCEND trial.

The UNLOAD study (138) compared the safety and efficacy of venovenous ultrafiltration with intravenous diuretics for hypervolemia in 200 patients with acute decompensated heart failure. In this small study, ultrafiltration produced a greater weight and fluid loss than diuretics, as well as a significantly reduced rehospitalization rate at 30 days. However, there was a nonsignificant signal for increased creatinine during all phases of hospitalization (although not for progression to dialysis). In addition, the results were based on very few clinical events. As such, the ongoing CARdiorenal REScue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, a National Institutes of Health study evaluating this strategy in fluid-overloaded heart failure patients with cardiorenal syndrome, will provide a more definitive answer to this question.

CONCLUSIONS

Several clinical syndromes of heart failure exist, the therapy of which are supported by a large body of evidence from randomized and observational clinical trials. However, many uncommon heart failure syndromes also occur, some of which involve the care of overlapping subspecialty providers. Together, these comprise a significant percentage of heart failure syndromes that should be addressed in consensus guideline statements to define and refine best practice approaches to their care. Despite the relative paucity of evidence from which to make recommendations, all patients with heart failure deserve access to a high quality of care, which includes delineation of when referral to appropriate subspecialty care is needed. Device therapy for patients with heart failure continues to evolve, with much work left to further clarify who will benefit from this potentially powerful therapy. Best practices continue to be refined according to evidence from important and landmark clinical trials, irrespective of whether that reinforces current care or leads to the introduction of new therapies.

The present guideline paper represents the commitment of the CCS to recognize heart failure as a major health care challenge, and to provide advice and resources to help meet that challenge. The publication has addressed important issues for which fewer clinical trails have been published but in which many clinical trials are needed. Some material could not be included in the manuscript and additional information, resources and tools will be published on the CCS heart failure guideline Web site (www.hfcc.ca). The present update is intended to support a CCS goal, which is to help achieve a measurable improvement in cardiovascular care and outcomes for Canadians.

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