Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers

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JMO Arnold, JG Howlett, P Dorian, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. Can J Cardiol 2007;23(1):21-45.

Heart failure is common, yet it is difficult to treat. It presents in many different guises and circumstances in which therapy needs to be individualized. The Canadian Cardiovascular Society published a comprehensive set of recommendations in January 2006 on the diagnosis and management of heart failure, and the present update builds on those core recommendations.

Based on feedback obtained through a national program of heart failure workshops during 2006, several topics were identified as priorities because of the challenges they pose to health care professionals. New evidence-based recommendations were developed using the structured approach for the review and assessment of evidence adopted and previously described by the Society. Specific recommendations and practical tips were written for the prevention of heart failure, the management of heart failure during intercurrent illness, the treatment of acute heart failure, and the current and future roles of biomarkers in heart failure care.

Specific clinical questions that are addressed include: which patients should be identified as being at high risk of developing heart failure and which interventions should be used? What complications can occur in heart failure patients during an intercurrent illness, how should these patients be monitored and which medications may require a dose adjustment or discontinuation? What are the best therapeutic, both drug and nondrug, strategies for patients with acute heart failure? How can new biomarkers help in the treatment of heart failure, and when and how should BNP be measured in heart failure patients?

The goals of the present update are to translate best evidence into practice, to apply clinical wisdom where evidence for specific strategies is weaker, and to aid physicians and other health care providers to optimally treat heart failure patients to result in a measurable impact on patient health and clinical outcomes in Canada.

Mise à jour des recommandations issues de la Conférence de 2007 de la Société canadienne de cardiologie pour un consensus sur l'insuffisance cardiaque : Prévention, prise en charge lors de maladie intercurrente ou de décompensation aiguë et utilisation des biomarqueurs

L'insuffisance cardiaque est fréquente et pourtant, elle reste difficile à traiter. Elle se manifeste sous des formes et dans des circonstances diverses, ce qui requiert une individualisation du traitement. La Société canadienne de cardiologie a publié en janvier 2006 une série complète de recommandations sur le diagnostic et la prise en charge de l'insuffisance cardiaque et la présente mise à jour se veut donc une version augmentée de ces recommandations de base.

Selon les commentaires obtenus par le biais d'un programme national d'ateliers sur l'insuffisance cardiaque tenus en 2006, plusieurs priorités ont été dégagées en raison des défis qu'elles représentent pour les professionnels de la santé. De nouvelles recommandations fondées sur des preuves ont été rédigées selon une approche structurée de révision et d'évaluation des preuves retenues, préalablement décrite par la Société. Des recommandations et des conseils pratiques spécifiques ont été mis de l'avant pour la prévention de l'insuffisance cardiaque, sa prise en charge lors de maladie intercurrente, le traitement de l'insuffisance cardiaque aiguë et les rôles actuels et futurs des biomarqueurs dans le traitement de l'insuffisance cardiaque.

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Received for publication December 11, 2006. Accepted December 12, 2006.

Les questions cliniques spécifiques abordées ont notamment été les suivantes. Comment détermine-t-on quels patients sont exposés à un risque élevé à l'égard de l'insuffisance cardiaque et quelles interventions doit-on appliquer? Quelles sont les complications susceptibles de survenir chez les insuffisants cardiaques présentant une maladie intercurrente? Comment ces patients doivent-ils être surveillés et quels médicaments devraient être ajustés ou cessés? Quelles sont les meilleures stratégies thérapeutiques pharmacologiques ou non pharmacologiques pour les patients qui souffrent d'insuffisance cardiaque aiguë? Comment les

nouveaux biomarqueurs peuvent-ils aider au traitement de l'insuffisance cardiaque et à quel moment et de quelle manière doit-on mesurer le BNP chez les insuffisants cardiaques.

Les objectifs de la présente mise à jour sont d'assurer l'application pratique des preuves les plus concluantes, de promouvoir le jugement clinique lorsque certaines stratégies spécifiques sont moins fructueuses et d'aider les médecins et autres professionnels de la santé à traiter le mieux possible les patients atteints d'insuffisance cardiaque de manière à exercer un impact mesurable sur la santé des patients et sur les résultats cliniques au Canada.

The Canadian Cardiovascular Society (CCS) has committed to a multiyear process of consensus conference panels to review evidence on topics of importance to the Canadian cardiovascular community. Heart failure was identified as the first topic to be rigorously reviewed within this mandate because it has a large burden on patients, families and health care resources, and also has a large body of clinical trial evidence to guide practice. A comprehensive set of evidence-based recommendations on the diagnosis and management of heart failure were published in January 2006 (1), and form the foundation on which the present 2007 update is based. The authors of the present update are the Primary Panel members, who were also responsible for identifying the scope of this review, reviewing the literature, determining relevance and strength of evidence, as well as formulating recommendations, which were agreed on by consensus. 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, <hfcc.ccs.ca>. In particular, care was taken to consider not just the health benefits, but also the possible side effects and risks associated with implementation of the recommendations. The Secondary Panel members reflect a broad spectrum of the Canadian cardiovascular community and reviewed the paper, providing constructive feedback to the Primary Panel.

The objective of the CCS Heart Failure Consensus Conference 2007 update is to provide Canadian clinical practitioners with evidence-based recommendations for the prevention of heart failure, the management of heart failure during intercurrent illness, the treatment of acute decompensated heart failure, and the current and future role of biomarkers in heart failure care. These topics were identified as priorities through ongoing needs assessments and evaluations provided by participants in the CCS National Heart Failure Workshop Initiative and were confirmed as priorities by the Primary Panel of the CCS consensus conference for heart failure. It is intended that the present update will complement the comprehensive paper published in 2006 (1), which focused on the diagnosis of new heart failure and the management of chronic heart failure. The clinical questions addressed by the current recommendations in the present paper include: which patients should be identified as being at high risk of developing heart failure and which interventions should be used? What complications can occur in heart failure patients during an intercurrent illness, how should these patients be monitored and which medications may require a dose adjustment or temporary discontinuation? What are the best therapeutic strategies for patients with an acute decompensation of heart failure? How can new biomarkers help in the treatment of heart failure, and when and how should natriuretic peptides (B-type or brain natriuretic peptides [BNP] and its prohormone [NT-proBNP]) be measured in heart failure patients? In addition, practical tips are provided to aid health care providers in the

management of their heart failure patients in circumstances that were not addressed in clinical trials and for which evidence-based recommendations cannot easily be made, but for which clinical experience and reports suggest a preferred approach to treatment. An extensive dissemination and implementation program has been developed for the CCS Heart Failure Consensus Conference Program. The CCS National Heart Failure Workshop Initiative is one aspect of this, but it has also been developed to involve Canadian clinical practitioners in the ongoing use and refinement of the CCS heart failure consensus conference process. Details of these and other initiatives, as well as the CCS 'closed-loop' model of consensus development may be found on the CCS Heart Failure Consensus Conference Program Web site.

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 trails 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.

2006 – THE YEAR IN REVIEW
Since the CCS heart failure recommendations were published in January 2006 (1), there have been many new publications and presentations. Some of these have been incorporated into this year's update, where appropriate, and others are noteworthy but not sufficient to change the 2006 recommendations or be included here as new recommendations. A selection of some of these areas and topics of interest are reviewed to provide additional background and understanding of the impact of heart failure on individuals and society.

Diastolic heart failure, or heart failure with preserved ejection fraction
Although diastolic heart failure (or heart failure with normal or preserved ejection fraction – different studies have different left ventricular ejection fraction [LVEF] and other definitions) is present in nearly 50% of hospitalized heart failure patients (2),

evidence to guide health care policies and resources has generally relied on epidemiological data from systolic heart failure and relatively little evidence exists from large-scale randomized trials on diastolic heart failure to guide our treatment selections.

Data from disease registries remind us of the poor outcomes for heart failure patients regardless of LVEF. In data from patients discharged from 103 Ontario hospitals in 2001 (3), 880 patients with LVEF greater than 50% were more likely to be older, female, and have atrial fibrillation and hypertension, but were less likely to have had a myocardial infarction compared with 1570 patients with LVEF lower than 40%. The one-year mortality rate was not significantly different compared with patients with a low LVEF. In data from 4596 patients with heart failure admitted to hospital in Olmstead County over a 15-year period from 1986 to 2001 (4), several baseline differences were seen among 2429 patients with low LVEF, defined as that lower than 50%, and 2167 patients with LVEF of 50% or greater. There was a slight advantage in survival in those with LVEF of 50% or greater (hazard ratio [HR] 0.96, 95% CI 0.92 to 1.00). In a smaller study of 556 inpatients and outpatients with heart failure in Olmstead County (5), echocardiography showed LVEF of 50% or greater to be present in 55% of patients and was associated with older age, female sex and no history of myocardial infarction. Echocardiographic evidence of isolated diastolic dysfunction with preserved LVEF was present in 44% of patients. Moderate or severe diastolic dysfunction was common in patients with reduced LVEF. At six months, age- and sex-adjusted mortality (16%) were the same for both preserved and reduced LVEF heart failure, although the study was not powered to test for differences in mortality. These data re-emphasize the importance of diastolic dysfunction in all patients with heart failure. Future studies are needed to determine which factors are most important in determining diastolic function and may help to understand the poor correlation between symptoms and systolic function in patients with heart failure.

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study was recently published (6). In this study, 850 patients 70 years of age and older with a diagnosis of heart failure, diastolic dysfunction by echocardiography and diuretic treatment, but without substantial LV systolic dysfunction or valve disease, were randomly assigned to either perindopril 4 mg or placebo for a minimum of one year after which follow-up frequency was according to investigator judgement (median follow-up 2.1 years). After one year, a large number of patients discontinued their assigned medication and most were started on an open-label angiotensin-converting enzyme (ACE) inhibitor. Treatment with perindopril over the entire duration of follow-up did not significantly reduce the primary end point of composite all-cause mortality and unplanned heart failure related admission (HR 0.92, 95% CI 0.70 to 1.21, P=0.55). During the first year of follow-up, there was a significant 37% reduction in heart failure hospitalizations and an improvement in 6 min walk test in the perindopril group. These results are not unlike those seen in the Candesartan in Heart failure – Assessment of Reductions in Mortality and morbidity (CHARM-Preserved) trial (7), in which a modest reduction in hospitalization, but not mortality, was seen with the angiotensin receptor blocker (ARB) candesartan.

Ahmed et al (8) reported the outcomes in 988 patients with LVEF of greater than 45% enrolled in the previously reported Digitalis Investigation Group (DIG) trial. Digoxin use was not associated with a reduction in death or all-cause hospitalization. There was a nonsignificant 21% reduction in heart failure hospitalization, which was offset by a nonsignificant 37% increase in hospitalization for unstable angina. These results suggest no role for the routine use of digoxin in heart failure patients with preserved LVEF who have normal sinus rhythm.

The use of beta-blockers is well established in systolic heart failure patients, but randomized data have been lacking for heart failure patients with preserved LVEF. The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) (9) randomly assigned 2128 elderly patients with either heart failure-related hospitalization in the past year or LVEF lower than 35% to nebivolol or placebo. More than one-third of patients had a baseline LVEF greater than 35%. The HR for the primary end point (all-cause death or cardiovascular [CV] hospitalization) in patients with LVEF greater than 35% (HR 0.82, 95% CI 0.63 to 1.05) was similar to the overall group (HR 0.86, 95% CI 0.74 to 0.99) (P=0.04). There was a nonsignificant reduction of CV hospitalization with nebivolol in the overall group. In a separate retrospective study of 443 patients (10) admitted to a Dutch hospital with heart failure and preserved LVEF, 227 patients receiving beta-blockers at hospital discharge had lower mortality, even after correction for differences in baseline covariates (HR 0.57, P=0.01). These data provide increasing rationale to consider beta blockade for heart failure patients with preserved LVEF.

Prevention of heart failure
The Jikei heart study (unpublished data) investigated the addition of the ARB valsartan (average dose 75 mg) to optimal medical treatment in 3081 Japanese hypertensive patients whose blood pressure (BP) was under control (mean BP 139/81 mmHg). Most patients (67%) were taking calcium channel blockers, while 35% were taking ACE inhibitors and 32% were taking beta-blockers. The primary end point was a composite of CV morbidity and mortality, including stroke or transient ischemic attack, hospitalization for heart failure or angina, dissecting aneurysm of the aorta, lower-limb arterial obstruction, doubling of serum creatinine or transition to dialysis. The study was stopped early due to a highly significant 39% reduction in the primary end point, which included a significant 46% reduction in hospitalization due to heart failure (HR 0.54, 0.31 to 0.94, P=0.029). These as yet unpublished data tend to support the addition of ARB therapy to treated hypertensive Japanese patients, although it is unclear how these data may be extrapolated to other populations.

Acute heart failure
The typical approach to the treatment of acute heart failure (AHF) includes rapid diagnosis, intravenous diuretic and early consideration of vasodilator therapy. Two interesting studies that were reported this year, but have not yet been published, shed further light on the evolution of AHF diagnosis and management.

The randomized Ultrafiltration Versus Intravenous (IV) Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study compared ultrafiltration with with a proprietary device against usual care with intravenous diuretics in 200 patients hospitalized for AHF, and the results were presented at the American College of Cardiology meeting

TABLE 1
Risk factors for the development of heart failure

Hypertension*	Excessive salt intake
Ischemic heart disease*	Cardiotoxic agents
Diabetes mellitus*/the metabolic syndrome	Familial history/genetic markers
	Low ejection fraction*
Hyperlipidemia*	Impaired diastolic function
Smoking*	Left ventricular hypertrophy
Obesity	Elevated neurohormonal biomarkers
Older age	Abnormal electrocardiogram
Male sex	Increased cardiothoracic ratio
Ethnicity	Microalbuminuria
Physical inactivity	Elevated resting heart rate
Heavy alcohol use	

Most important targets for prevention

in March 2006. The patients were evaluated at 48 h and 90 days, and those randomly assigned to ultrafiltration lost more weight (5.0 kg versus 3.1 kg, P=0.001) and were less likely to be rehospitalized within 90 days (18 versus 32 patients readmitted, P=0.02). This promising therapy will be tested further in a phase III trial. The IMPROVE-CHF, a Canadian study of 501 patients, evaluated the diagnostic, clinical and cost outcomes associated with the addition of measuring NT-proBNP levels to usual clinical care in seven emergency departments. The use of NT-proBNP measurements was associated with positive clinical results (unpublished data). These results reinforce the increasingly important role of the measurement of natriuretic peptides in the diagnosis and management of acute decompensated heart failure.

Immune modulation therapy
Early reports had suggested that immune modulation may have significant clinical benefit in heart failure and other patient groups. The Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) study exposed a patient's own blood to specific oxidative stress then injected it intramuscularly into the same patient and the results were presented at the European Society of Cardiology meeting in September 2006 (unpublished data). In the study, 2408 patients with mild to moderate heart failure at 176 centres were randomly assigned to this monthly immune modulation therapy or placebo. The primary end point, all-cause mortality or CV hospitalization, was not different between the two groups, although post hoc analysis suggested a benefit in New York Heart Association (NYHA) functional class II patients. The significance of this finding, while interesting, is not known at present.

Enhanced external counterpulsation
The Prospective Evaluation of EECP in Congestive Heart failure (PEECH) trial (11) is the first randomized study of this therapy and involved 187 patients with mild to moderate heart failure. After six months of treatment, significantly more patients increased exercise time by more than 60 s in the treatment arm, but there was no difference in the more objective end point of peak oxygen consumption measurements. There was no difference in clinical events between the two groups. While the results of this study are interesting, the use of a subjective end point in a study that has inherent

blinding difficulties is difficult to interpret, and no recommendation can be made at this time until further randomized data become available.

PREVENTION OF HEART FAILURE
Patients at risk of developing heart failure
Recommendations
- Clinical assessment is recommended in all patients to identify known or potential risk factors for heart failure (eg, hypertension, ischemic heart disease, diabetes mellitus, hyperlipidemia and smoking) (class I, level C).

- All modifiable risk factors for heart failure, including those for coronary artery disease, such as hypertension, diabetes mellitus and hyperlipidemia, should be treated in accordance to current national guidelines (class I, level A).

Patients with asymptomatic LV dysfunction
Recommendations
- ACE inhibitors should be used in all asymptomatic patients with LV dysfunction and EF lower than 40% (class I, level A if EF lower than 35%; class I, level B if EF 35% to 40%).

- Beta-blockers should be considered in all patients with asymptomatic LV dysfunction and LVEF lower than 40% (if prior myocardial infarction class I, level B; if no myocardial infarction, class IIa, level C).

Strategies to prevent heart failure include both primary and secondary prevention. In primary prevention, the goal is to prevent the development of asymptomatic or symptomatic LV dysfunction in patients who have risk factors but no history of symptomatic heart failure. In secondary prevention, the goal is to reduce heart failure-related morbidity and mortality in patients who already have symptomatic heart failure. Recommendations for secondary prevention were addressed previously in the 2006 CCS consensus recommendations (1).

A number of factors have been documented as increasing the risk of heart failure (Table 1). Among these, hypertension, ischemic heart disease, diabetes mellitus, hyperlipidemia, smoking and obesity are the most important potential targets for the prevention of atherosclerosis and/or cardiac dysfunction. Moreover, in selected patients with multiple risk factors for heart failure, screening for ventricular dysfunction can identify individuals in whom more aggressive therapy is indicated. For patients found to have asymptomatic LV systolic dysfunction, early therapy with ACE inhibitors may decrease the subsequent risk of developing symptomatic heart failure and improve long-term survival (12,13).

Hypertension and LV hypertrophy
Hypertension has long been known to be a risk factor for heart failure. In the Framingham study (14), hypertension increased the risk of developing heart failure by two- to threefold. The risk appears to be continuous, with no clear threshold. Both diastolic and systolic dysfunction can arise in the setting of hypertension, with or without LV hypertrophy (15).

Treatment of hypertension clearly reduces the risk of heart failure development. The Blood Pressure Lowering Treatment Trialists' Collaboration, in a systematic review of 29 trials

involving 162,000 patients (16), showed that treatment with ACE inhibitors, ARBs, diuretics and beta-blockers reduced the risk of development of heart failure (defined as hospital admission or death from heart failure). In contrast, a calcium channel blocker-based regimen had no significant effects on the prevention of heart failure (RR 1.21, 95% CI 0.93 to 1.58) and was less effective than regimens based on diuretics, beta-blockers or ACE inhibitors (16).

LV hypertrophy is also associated with an increased risk of heart failure development (15,17). This risk is independent of its association with hypertension. Weight loss, sodium restriction, diuretics, beta-blockers, ACE inhibitors, ARBs and calcium channel blockers have been shown to reduce hypertrophy (15) and, presumably, the risk of developing heart failure.

Ischemic heart disease

Coronary artery disease has been cited as the cause of 52% of heart failure diagnoses in the general population (18). Approximately 40% of patients who experience a myocardial infarction will also experience heart failure over time (19). In patients with established heart failure, the occurrence of a new myocardial infarction increases the risk of subsequent death up to eightfold, with one-third of all deaths preceded by a major ischemic event (20). Similar data have also been reported in the Survival and Ventricular Enlargement (SAVE) trial (21). As such, preventive strategies for ischemic heart disease, such as those targeting dyslipidemia, hypertension, diabetes and smoking, are also effective in preventing heart failure.

Diabetes mellitus

Diabetes mellitus is a well-established risk factor for coronary artery disease. It is recognized, however, that diabetes mellitus may produce heart failure independently of coronary artery disease by causing a diabetic cardiomyopathy (15). Data from the National Health Examination Survey I (22) and the Framingham study (17) have shown the incidence of heart failure in patients with diabetes mellitus to be two- and fourfold higher, respectively, than in patients without diabetes mellitus. While an increase in glycosylated hemoglobin (HbA1C) among patients with diabetes mellitus is a recognized risk factor for heart failure (23-27), no study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (28). The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (29) recommends that most patients with type 1 or type 2 diabetes be targeted to achieve an HbA1C level of 7.0% or lower.

Hyperlipidemia

Both an elevated triglyceride level and a high ratio of total to high-density lipoprotein cholesterol have been found to be associated with an increased incidence of heart failure (30). In addition, retrospective analyses of clinical trial data have supported the role of statins in preventing heart failure (31). Data from the Scandinavian Simvastatin Survival Study (4S [32]) showed that only 8.3% of patients who received simvastatin were diagnosed with heart failure during follow-up, compared with 10.3% of patients who received placebo. In a cohort of elderly patients with prior myocardial infarction and low-density lipoprotein cholesterol of 3.2 mmol/L or higher, those who were receiving statin therapy had a 26% RR reduction for developing heart failure (33).

Both the 2006 CCS position paper (34) on the recommendations for the diagnosis and treatment of dyslipidemia and prevention of CV disease, and the 2001 National Cholesterol Education Program report (35) on the detection, evaluation and treatment of high blood cholesterol in adults have provided detailed guidelines for the screening, risk assessment, diagnosis and treatment (pharmacological and nonpharmacological) of dyslipdemia.

Smoking

Cigarette smoking was found in 42% of men and 24% of women who developed heart failure in the Framingham study (36). In men, the relationship between cigarette smoking and the development of heart failure was greatest in the younger age group (30). In women, the relationship was less consistent, although there was a trend toward an increase in RR among older women (36). The National Health and Examination Survey I (22) demonstrated that smoking accounted for approximately 17% of all incident cases of heart failure. The Heart and Estrogen/Progestin Replacement Study (HERS [37]) showed smoking to be a predictor for the development of heart failure in women with established heart disease. A direct and independent relationship has been observed between smoking and the development of asymptomatic ventricular dysfunction (38-40). A dose-response relationship has also been found between the number of pack-years of smoking and reduced regional LV function in asymptomatic individuals (40). Quitting smoking can result in, within two years, a 30% reduction of mortality and morbidity among heart failure patients (41).

Obesity

In 2004, Statistics Canada reported that 36% of Canadians 18 years of age and older have a body mass index of 25 kg/m^2 or higher (ie, overweight), and 23% have a body mass index of 30 kg/m^2 or higher (ie, obese) (42). Overweight and obesity have been identified as independent risk factors for heart failure (22,43-45). Changes in LV structure and function have been documented in both overweight and obese individuals without overt heart disease, regardless of BP, age, sex and LV mass (46-48). Weight loss following bariatric surgery in morbidly obese heart failure patients has been associated with decreases in LV mass, as well as improvements in LV systolic function and diastolic filling (47,49,50). Reversal of heart failure after weight loss by dietary means has been described in a morbidly obese patient (51).

Microalbuminuria

Microalbuminuria is an independent risk factor for heart failure; the risk is highest for patients with concomitant risk factors such as diabetes mellitus. Among diabetic patients with no prior history of heart failure, the presence of elevated urinary albumin excretion increased the risk of heart failure by two- to fourfold (25,52). In both diabetics and nondiabetics, increasing the urinary albumin to creatinine ratio conferred a stepwise increase in the risk of heart failure development (52).

Although there is good evidence that microalbuminuria increases heart failure risk, current data are insufficient to support the treatment of microalbuminuria to prevent heart failure. The Heart Outcomes Prevention Evaluation (HOPE) study and the Microalbuminuria, Cardiovascular and Renal

Outcomes-HOPE (MICRO-HOPE) substudy showed that ramipril significantly reduced urinary albumin excretion (53) and decreased the risk of new-onset heart failure (54). Caution is needed when interpreting such data, because any association in risk reduction between microalbuminuria and heart failure may be confounded by other clinical indications for ACE inhibitor use in the trial. In the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT [55]), which primarily targeted the treatment of microalbuminuria wherein patients with confounding indications for ACE inhibitor use were excluded, fosinopril did not reduce the risk of heart failure, despite a 26% reduction in urinary albumin excretion.

Screening for LV dysfunction

There is currently no consensus on the optimal screening method that accurately detects asymptomatic LV dysfunction and is cost-effective in reducing the population burden of heart failure. Community-based epidemiological surveys of individuals without a prior history of heart failure have documented a prevalence of 1% to 6% with impaired systolic function (56) and 11% to 21% with isolated impaired diastolic function (57,58). Both circulating neurohormonal biomarkers and transthoracic echocardiography have been evaluated as screening tools. Elevated plasma levels of BNP and to a lesser extent, NT-atrial natriuretic peptide and NT-proBNP, have been used to detect ventricular dysfunction (59). In community-based screening that used cut-off levels of greater than 18 pg/mL to 65 pg/mL to detect asymptomatic LV systolic dysfunction, BNP level was not consistent in either its sensitivity nor specificity to be an accurate screening tool when used in isolation (56). Caution is also advised against using a single cut-off value, because levels of natriuretic peptides are known to be influenced by age (60), sex (60) and lean body mass (61). Moreover, BNP levels cannot reliably differentiate between systolic and diastolic dysfunction (62). By contrast, parameters of systolic and diastolic ventricular function known to be predictive of heart failure risk are readily detectable by echocardiography (63). However, echocardiography is too impractical and expensive at present to be used as an initial screening tool in a community setting.

In an attempt to address the limitations inherent in any single screening test, sequential screening has been proposed and aims to combine a relatively inexpensive initial test (such as a 12-lead electrocardiogram [ECG] or biomarker) with the more costly confirmatory test (echocardiography) in a multistaged strategy (64). Unfortunately, the low specificity of these initial tests necessitates the subsequent use of confirmatory tests that are too frequent to be practical. For example, using BNP levels to initially screen for asymptomatic ventricular dysfunction in the community would necessitate echocardiography in 10% to 40% of those screened, but would still miss 10% to 60% of those affected (62).

As an alternative to general screening, selective screening has been suggested for patients in the community who are identified to be at higher risk for asymptomatic ventricular dysfunction (65). Subgroups at highest risk include those with ischemic heart disease, hypertension and diabetes mellitus (66), as well as certain ethnic groups (67,68) and the elderly (69).

Practical tips:
- BP should be controlled to less than 140/90 mmHg in most individuals and less than 130/80 mmHg in those with diabetes and/or kidney disease.

- In high-risk patients with multiple risk factors for heart failure, it may be useful to reduce BP even if it is already within the normal range.

- Patients with diabetes mellitus should have their glycemic control optimized to an HbA1C level of 7.0% or lower.

- Hyperlipidemia should be treated aggressively with lipid-lowering drugs, especially statins. In high-risk patients for heart failure, a target level below 2.0 mmol/L for low-density lipoprotein cholesterol may be appropriate.

- Smoking cessation and weight reduction for overweight or obese individuals are important preventive strategies for heart failure.

- Patients at high risk for developing heart failure should be immunized against influenza (yearly) and pneumococcal pneumonia (if not received in the past six years).

- Poor adherence to preventive measures is common; therefore, patients should be reassessed regularly to achieve and maintain the recommended targets.

- Routine screening for asymptomatic LV dysfunction is not recommended. For selected patients with multiple risk factors at high risk for heart failure, the decision to screen (such as by echocardiography) should be individualized (Table 2).

PATIENTS WITH HEART FAILURE AND INTERCURRENT ILLNESS

Heart failure is an increasingly common condition in North America, with a lifetime risk of approximately 20% for those 40 years of age and older (70). Because heart failure incidence and prevalence increase with advancing age, heart failure is also more likely to occur in the setting of other significant illnesses. Indeed, the average patient with heart failure suffers from five or six concomitant medical conditions (71). Patients with increased comorbid disease burden, especially when elderly and hospitalized, are less likely to be enrolled in randomized clinical trials, and as such, have not been specifically addressed in previously published heart failure guidelines.

Because major clinical trial data are lacking in this area, the following recommendations on selected conditions of common interest to those treating heart failure patients have relied in large part on results from systematic and self-directed literature review, which predominantly included small, randomized trials, observational data, retrospective data reviews and expert consensus opinion based on extensive clinical experience.

TABLE 2
Causes and precipitating factors in acute heart failure

Decompensation of pre-existing chronic heart failure

Precipitating factors:

- noncompliance with treatment or diet (fluid and salt restriction or medication use)
- inappropriate use of medications (prescribed or over-the-counter, including natural agents)
- infections
- arrhythmias or ischemia
- deterioration of renal function
- drug or alcohol abuse
- after noncardiac surgery (volume overload)
- pheochromocytoma

Acute coronary syndromes

Precipitating factors:

- myocardial infarction/unstable angina with large extent of ischemia and ischemic dysfunction
- mechanical complication of acute myocardial infarction
- right ventricular infarction

Hypertensive crisis

Arrhythmia (ventricular tachycardia or fibrillation, atrial fibrillation or flutter, supraventricular tachycardia or severe bradycardia)

Valvular regurgitation (endocarditis, rupture of chordae tendinae, etc)

Severe aortic valve stenosis

Acute myocarditis

Cardiac tamponade

Aortic dissection

Postpartum cardiomyopathy

High-output syndromes

Precipitating factors:

- septicemia
- thyrotoxicosis crisis
- anemia
- presence of shunt

Adapted from Ghali (148)

Heart failure in the elderly
Recommendation

- Elderly or frail heart failure patients who present with acute illness should be assessed for evidence of delirium and, before discharge, cognitive impairment (class IIa, level C).

A relatively simple score can be used to characterize frail elderly patients who are clinically stable (72) (Figure 1). It may be useful to identify high risk patients who require more careful and detailed development of a multidisciplinary care plan. When frail elderly patients present with either an exacerbation of heart failure itself or another medical condition, they often appear confused. This may be due to acute delirium, chronic dementia or a combination of both. The relative contributions of each may be difficult to determine during acute illness, and may become apparent only when the aggravating illness(es) is controlled. Delirium should be suspected in the setting of an acute illness accompanied by an altered and fluctuating level of consciousness and/or cognition, and can be screened for using available tools (73,74). In many cases,

Figure 1) *The Canadian Study of Health and Aging (CSHA) clinical frailty scale*

discussion and development of complex treatment plans are delayed or made increasingly difficult when evidence of patient cognitive impairment becomes apparent. In addition, cognitive impairment may persist well beyond the resolution of the acute precipitating illness. To screen for persistent cognitive impairment in stable patients, several instruments have been developed that require varying degrees of time, effort and expertise to administer. The Mini Mental Status Examination, requires approximately 20 minutes to administer. It has been validated, and is moderately sensitive and specific, although some aspects of executive function are not well identified (75). The Montreal Cognitive Assessment test (76) has been developed to specifically identify mild cognitive impairment, especially if related to vascular disease, and is endorsed by the Canadian Stroke Network. It requires little training to administer and the short form may be performed in about 5 min. This short form includes the Montreal Cognitive Assessment subtests (five word memory task tests – registration, recall, recognition – six item orientation tests and one letter phonemic fluency test) and can be downloaded free for noncommercial purposes at <www.mocatest.org> (76). Because these instruments have been validated in medically stable patients, they may be best used once the heart failure patient is stabilized to choose appropriate care plans and discharge planning. Other instruments, according to the clinical need (ie, screening, documentation of mental status, complete neuropsychiatric evaluation), may be found in the National Institute of Neurological Disorders publication (75).

Practical tip:

- In a hospitalized elderly or frail heart failure patient, screening for chronic cognitive impairment is best performed pre-discharge once the patient has been stabilized.

Heart failure and treatment of diabetes
Recommendation
- Elevated blood glucose in patients with heart failure should be treated according to current Canadian Diabetes Association guideline recommendations – aim for a target HbA1C level of 7.0% or fasting/preprandial blood glucose of 4.4 mmol/L to 7.0 mmol/L (class I, level A).

Diabetes is present in more than one-third of patients with heart failure. Treatment choices involve dietary therapy, metformin, thiazoladinediones, biguanides, sulphonylureas and insulin, all of which have their own advantages and disadvantages.

Metformin is an effective oral antidiabetic agent. Due to the presumed effects on pyruvate metabolism, metformin is approved for use under the 'black box' warning in the setting of 'hypoxic' conditions, such as renal insufficiency, congestive heart failure, liver disease and chronic obstructive pulmonary disease (COPD). This warning is based on isolated case reports and a biochemical rationale that these conditions predispose patients to lactic acidosis (a condition associated with decreased serum bicarbonate levels), anion gap acidosis and systemic lactate level greater than 5 mmol/L, with a mortality of 40% to 60%. In addition, two large meta-analyses and a smaller case series (77-79) have evaluated the outcomes and occurrence of lactic acidosis associated with use of metformin compared with placebo (nonrandomized) or other antidiabetic agents, such as sulphonylureas and insulin. The combined number of patients was in excess of 40,000 and included those with heart failure, COPD and renal disease. There was no increase in the occurrence of lactic acidosis and, in addition, CV outcomes of patients with heart failure taking metformin were better than those taking other antidiabetic therapies. While a precise renal function cut-off point for use of metformin was not apparent from these data, in general, only those with a serum creatinine level up to 150 µmol/L were included in the meta-analyses and those with serum creatinine levels up to 200 µmol/L were included in a smaller, single-centre study.

Current evidence suggests that patients with heart failure and/or mild to moderate renal dysfunction (estimated glomerular filtration rate [eGFR] greater than 30 mL/min which correlates reasonably with a serum creatinine greater than 150 µmol/L in women and greater than 180 µmol/L in men unless at extremes of age or body weight) fare at least as well, if not better, with metformin than with other antidiabetic agents, and metformin should still be considered as first-line therapy in heart failure patients with mild to moderate renal dysfunction (77-79).

Thiazolidinediones are known to cause fluid retention, although this is generally mild. Recent studies suggest this is not a direct toxic effect on the myocardium. The recently reported Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study (80), in which pioglitazone was given to diabetic patients at risk for cardiac ischemic events, showed that thizoladinedione was associated with fewer cardiac ischemic events, but at the cost of an increase in heart failure hospitalizations (2% absolute excess over 2.8 years, or less than 1% per year). The recently completed Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study (2×2 factorial design) tested whether development of diabetes could be prevented by rosiglitazone and/or ramipril. In more than 5000 patients, a significant reduction of new glucose intolerance and CV events (absolute 0.8% reduction) was seen with rosiglitazone, but a small excess of new-onset heart failure was also observed (absolute 0.4%) (81), similar to the the PROACTIVE study. A recently completed randomized trial that compared the efficacy of rosiglitazone, metformin or glyburide monotherapy in type 2 diabetics reported a significantly greater failure rate of monotherapy with glyburide or metformin than with rosiglitazone, but showed an increase in reported heart failure with rosiglitazone. When only adjudicated events were considered, there was no significant difference in CV- or heart failure-related mortality in any arm (82). Recent reports suggest that the fluid retention with this drug class may be safely managed with careful observation, taking care not to increase diuretic therapy in the absence of either symptoms or signs of central volume overload (rather than just peripheral edema) (78,79). As such, this medication remains a viable choice in stable heart failure patients without fluid retention, but such patients should be followed more closely for signs of fluid retention and pulmonary congestion.

Practical tips:
- Metformin may be considered a first-line agent for diabetes treatment if the eGFR is greater than 30 mL/min. However, care should be taken to temporarily discontinue metformin if renal function worsens significantly.

- Oral antidiabetic therapy should be individualized; however, no compelling evidence exists to recommend one agent over another.

Heart failure with renal dsyfunction
Recommendations
- Heart failure patients with stable renal function (serum creatinine levels less than 200 µmol/L) should receive standard therapy with an ACE inhibitor, ARB or spironolactone, but monitoring of serum potassium and creatinine levels should be more frequent, especially if combination therapy is used or in the case of an acute concomitant illness that causes dehydration (class I, level B).

- Patients with heart failure who continue to experience volume overload or increasing serum creatinine levels should be assessed for reversible causes such as concomitant medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]), hypovolemia, hypotension, urinary tract obstruction or infection (class I, level C).

- The indications for the use of digoxin should be re-evaluated in heart failure patients with severe renal dysfunction; the trough digoxin level (at least 8 h after a dose) should be checked, and the dose should be adjusted to maintain a trough level less than 1 nmol/L. For patients with more rapid deterioration in renal function, digoxin should be withheld and re-evaluated once renal function has stabilized (class I, level C).

- In oliguric heart failure patients who are hemodynamically stable, diuretics, ACE inhibitors, ARBs, spironolactone and nonheart failure drugs that impair renal function should be reviewed daily (class I, level C).

- In stable heart failure patients who are not oliguric but have increasing serum creatinine levels of more than 30% from a previous stable baseline, the dose of diuretics, ACE inhibitors, ARBs and spironolactone may be reduced until renal function stabilizes (class 1, level C).

- Routine use of ACE inhibitors, ARBs or spironolactone in the setting of severe renal dysfunction (serum creatinine levels greater than 250 µmol/L or an increase of more than 50% from baseline) is not routinely recommended due to a lack of evidence for efficacy in heart failure patients (class IIa, Level C).

- In heart failure patients not responding adequately to more than 240 mg intravenous furosemide daily, treatment options include:
  - More frequent or higher doses of intravenous boluses of diuretic (class IIb, level C);
  - Combination with thiazide diuretic, eg, hydrochlorothiazide or metolazone (class IIA, level B); or
  - Continuous intravenous furosemide infusion (class IIa, level B).

The importance of renal dysfunction in the setting of heart failure is increasingly being recognized (83,84). Several studies have shown renal function to be one of the strongest predictors of adverse outcomes in heart failure patients (84-86). In general, adverse CV events increase once eGFR falls below 60 mL/min (83). In AHF, increasing creatinine levels by as little as 30 µmol/L during hospitalization is associated with prolonged hospital stay, as well as early and late mortality (87). Renal dysfunction is typically multifactorial, and is frequently related to poor renal perfusion, vascular disease and effects of chronic hypertension and medications (NSAIDs and others), as well as diabetes and intrinsic renal disorders. In addition, renal dysfunction and heart failure tend to exacerbate each another, leading to a cycle of further worsening volume overload, peripheral vasoconstriction and hypoxia, followed by further deterioration of renal blood flow (cardiorenal syndrome). Erythropoietin, produced by the kidney, is critical to hemoglobin synthesis. Relative erythropoietin resistance is seen in heart failure, which results in anemia that can further aggravate renal dysfunction, and is a significant and independent predictor of outcomes; increased risk is generally present with hemoglobin levels less than 110 g/L to 120 g/L or hematocrit less than 35%.

It is important to recognize worsening renal function early because there is a critical time period during which correction of reversible causes may re-establish stability. Several reversible factors frequently contribute to worsening renal function. The most important are systemic hypotension and volume depletion. In addition, concomitant drugs may contribute if they have a risk for adverse renal effects such as renin-angiotensin-aldosterone system inhibitors, ARBs and spironolactone, hypotensive agents (especially vasodilators), NSAIDs and cyclooxygenase 2 inhibitors (88,89). Systemic factors such as sepsis and urinary obstruction (especially chronic) are also important.

In general, mild fluctuations in renal function are common in heart failure patients, but these usually do not exceed 30% of the baseline creatinine level and should simply be observed. However, oliguria or larger increases in serum creatinine levels should prompt action and increased surveillance. In a subset of patients with increased creatinine levels and severe volume overload, diuresis may actually result in improved renal function, presumably due to a left shift from the extreme right of the Starling curve, which allows stroke volume to increase.

Patients with AHF require volume removal to relieve congestion and improve symptoms. Many patients respond promptly to intravenous furosemide in doses ranging from 40 mg to 120 mg, likely as a result of improved bioavailability. However, many patients do not respond to intravenous furosemide unless very high doses are used, a situation usually referred to as diuretic resistance. Several potential causes may underlie this important problem, such as magnesium or potassium deficiency (due to chronic loss from diuretics), severe reduction in GFR leading to excessive sodium resorption in the distal tubule, poor renal perfusion and reduced cardiac output, anemia and excessive vasodilation (85,86,90,91). To combat this, several strategies have been developed, such as repeated administration (often better than a large single dose) or addition of a thiazide-type diuretic to inhibit distal sodium resorption (92-98). Furosemide infusion is superior to, and at least as safe as, repeated large-dose boluses (95,99-103). A disadvantage of intravenous infusions is that many hospitals mandate that such infusions be given in intermediate or even intensive care settings.

Some small studies suggest that simultaneous administration of hypertonic saline with intravenous furosemide enhances diuresis while limiting the risk of hyponatremia (95). This is not a widely used strategy and should only be used under the supervision of a physician with extensive expertise in its application. Several small studies have shown that ultrafiltration (slow continuous venovenous method or traditional dialysis) can be very effective in fluid removal and symptom improvement in a few highly selected patients with severe renal insufficiency and volume overload (104-108). These seem to be most effective when renal function is severe but stable, rather than acute. This should be performed in consultation with a nephrologist or a specialist physician who has experience using ultrafiltration and in a setting of close inpatient observation.

Re-evaluation of medical therapy and drugs remains important in any situation of changing volume status. Thus, with any significant diuretic adjustment (especially intensification) repeat measurement of electrolytes and creatinine levels is suggested within at least seven days. In the setting of advanced heart failure, assessment should be within one to three days. It is also not uncommon for patients with a dehydrating illness to become volume-depleted, with associated electrolyte abnormalities, even when asymptomatic. This particularly occurs in elderly population. Measurement of renal function and electrolytes is therefore suggested in the setting of any acute dehydrating illness (85,89-91). Patients who improve with evidence-based heart failure therapy, especially with beta-blockers, may experience diminishing requirements for diuretics.

Practical tips:
- Acute renal dysfunction would generally be diagnosed when serum creatinine levels increase by more than

30% of baseline value over several days or when oliguria and rising serum creatinine are present. In this situation, volume status and clinical perfusion in heart failure patients must be carefully and repeatedly assessed, and this includes body weight, urine output, BP, serum electrolytes and renal function. These should be reviewed daily in hospitalized patients.

• In the setting of worsening renal function, heart failure patients should be followed closely. Volume-overloaded patients who do not respond to bolus intravenous furosemide may respond much more favourably to continuous furosemide infusion.

• In highly selected cases and under experienced supervision, hypertonic saline, in combination with a high-dose loop diuretic or intermittent slow continuous venovenous ultrafiltration, may be considered.

• When diuretics are reduced, especially in the setting of a concomitant ACE inhibitor, ARB or spironolactone, serum electrolytes should be rechecked within two to four weeks to assess serum potassium levels (109).

Heart failure patients with anemia
Recommendation
• Patients with heart failure and anemia (plasma hemoglobin less 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 deficiencies should be treated (class I, level C).

Anemia is a frequent and significant contributor to symptoms and adverse events in patients with heart failure. In many cases, the etiology of the anemia is related to chronic disease, both the heart failure itself and often renal insufficiency. While the optimal hemoglobin level is not known, increased adverse events are seen when the plasma hemoglobin level is lower than 110 g/L or hematocrit lower than 35%. The increased event rate seems to be inversely related to hemoglobin below these levels (110-112).

Early clinical trials have been performed with bone marrow-stimulating agents, such as erythropoietin and darbepoetin, in patients with heart failure (LVEF usually between 35% and 40%) and anemia. To date, studies such as the recently reported (but not yet published) Study of Anemia in Heart Failure-Heart Failure Trial (STAMINA-HeFT) suggest an improvement in symptoms and treadmill exercise time, but an uncertain effect on death and hospitalization. Similar strategies for patients with chronic kidney disease but without heart failure have also not shown benefit (113). It has been suggested that increasing hemoglobin aggressively may be associated with thrombotic events. The ongoing, multicentre, randomized study, Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF), will address these issues and is powered for morbidity and mortality.

Practical tips:
• Heart failure patients with severe anemia should be assessed by a physician who is experienced in the diagnosis and management of anemia, and underlying

causes should be treated using intravenous means, if necessary.

• There is currently insufficient evidence to support the routine use of bone marrow-stimulating drugs to increase hemoglobin levels in heart failure patients.

• In general, plasma hemoglobin levels lower than 90 g/L are associated with increased symptoms of heart failure. In this setting, consideration may be given to blood transfusion or a bone marrow-stimulating agent if advanced symptoms are present and after substrate deficiencies have been corrected.

Heart failure and acute intercurrent medical illness
Recommendations
• Beta-blockers should be initiated as soon as possible after diagnosis of heart failure, including during the index hospitalization, provided that the patient is clinically stable. Clinicians should not wait until hospital discharge to start a beta-blocker in stabilized patients (class I, level B).

• Beta-blockers should be continued in patients hospitalized with AHF, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia (class IIa, level C).

• Beta-blockers and ACE inhibitors should be continued at their usual dose during acute intercurrent illness (eg, pneumonia, exacerbation of COPD, other systemic infection, etc), unless they are not tolerated (eg, if significant reactive airways disease is present) (class IIa, level C).

• In a life-threatening complication, beta-blockers and ACE inhibitors or ARBs may be discontinued abruptly, but generally, if there is concern about their use, the dose should be decreased by one-half, and the patient should be reassessed. If the dose is reduced, it should be uptitrated to the previous well-tolerated dose as soon as safely possible (class IIa, level C).

• Heart failure patients with an acute dehydrating illness of any kind should undergo prompt evaluation and measurement of serum electrolytes, as well as blood urea nitrogen (BUN) and creatinine levels, even if not clinically volume-overloaded or -depleted. They should also be followed carefully until they return to their previous health state (class IIa, level C).

• In an acute dehydrating illness with risk of worsening renal function, spironolactone may be temporarily withheld because hyperkalemia is more common in this setting (class I, level C).

• Colchicine should be considered for acute gouty attack in heart failure patients. An oral or intra-articular steroid may also be considered (class IIa, level C).

- When noncardiac surgery requiring general anesthesia is contemplated, patients with heart failure should be evaluated preoperatively by a physician experienced in heart failure management (class I, level C).

Initial recommendations for beta-blockers in heart failure patients with systolic dysfunction stipulated that they be used in clinically stable outpatients (114). Recent studies have shown that it is safe to initiate beta-blockers in hospital, provided the patient is clinically stable (111,112,114,115). Data from the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (116) of patients with severe systolic heart failure showed that patients tolerated the beta-blocker carvedilol better than placebo while hospitalized and during the first month of therapy. Patients who are prescribed beta-blockers in hospital are more likely to be on treatment in the intermediate follow-up and are more likely to be at target doses without an increase in side effects or adverse events (117). This supports a strategy of beta-blocker administration before hospital discharge in stabilized patients (117-126).

A recent substudy of the DIG trial (127) reported that heart failure patients who were on beta-blockers at hospital admission had lower morbidity and mortality than those not on beta-blockers. Patients with decompensated heart failure who continue beta-blockers have improved hemodynamic and heart rate response to dobutamine, and demonstrate less ventricular ectopy/tachycardia (119,120) compared with those not continued on beta-blockers. This is consistent with the notion that beta blockade upregulates the $beta_1$-receptor in myocardium and suggests that these patients have the capacity to respond to inotropic infusion at least as well, if not better than, if beta blockade is not present. No study to date has suggested that the administration of a beta-blocker at hospital admission predisposes patients to cardiogenic shock. This is in contrast to the acute intravenous administration of a beta-blocker to naïve patients in the acute myocardial infarction setting. There are no data regarding the use of beta blockade in cardiogenic shock because in most cases, clinicians will withhold in this setting (100,106-113,128).

Accumulated data now suggest that beta blockade is well tolerated and associated with improved outcomes in patients with COPD unless reactive airways disease is present (a greater than 20% response to bronchodilators or a clinical history of asthma). There is no other subgroup of patients that has been shown to experience increased adverse events or side effects (117-126).

Patients with heart failure are at increased risk of gout due to low cardiac output, reduced renal function, chronic loop diuretic use and possibly increased total body water fluctuation. The standard therapy treatment for gouty arthritis, NSAIDs or cyclooxygenase 2 inhibitors, have known adverse renal effects and are associated with increased hospitalizations (and possibly death) in patients with heart failure (88,129-132). They should, therefore, be avoided when other adequate treatments are available. Oral colchicine is an effective therapy and is generally safe to use in heart failure patients. Alternatively, a short-term oral steroid for one to two weeks or an intra-articular steroid (when feasible, such as with a certain single joint involvement) may be used for a lower level of fluid retention and other side effects (133). Allopurinol may be started approximately two weeks after the acute episode is completed. Small studies have hypothesized that allopurinol may be beneficial in chronic heart failure,

possibly due to its antioxidant properties, although this is has not been proven (84,129-131,134).

Previously published risk scores to estimate cardiac morbidity and mortality for noncardiac surgery have included heart failure as an important risk factor (135). Heart failure patients with planned urgent noncardiac surgery have a lower than 10% risk, but this is still approximately double the risk of other patients with similar comorbid burden. One large series of patients (136) reported a 12% perioperative mortality and 20% hospital readmission within 30 days of urgent noncardiac procedures. Patients with heart failure should undergo electrocardiographic and vital sign monitoring, typically in a step-down or intensive care setting (depending on the severity of heart failure, type of intervention and urgency of procedure) for up to 48 h following operative intervention. In these patients, collaboration with the attending surgeon and anesthetist is recommended to offer an unambiguous care plan. When possible, intravenous fluid administration during the operative procedure should be limited as much as possible to prevent development of volume overload postoperatively. The fluid and electrolyte balance should be carefully followed during the recovery phase and until the patient is clinically stable from both a surgical and heart failure perspective. If possible, all usual heart failure medications should be administered before and after noncardiac surgery, with the possible exception of diuretics in the stable patient without volume overload (135-137). While preoperative stress testing is usually recommended for patients with ischemic heart disease, no clear benefit has been shown with the routine use of intraoperative, invasive, central hemodynamic monitoring (pulmonary artery catheter) or transesophageal echocardiography (Figure 1) (138,139).

AHF
Definitions and diagnosis of patients with AHF
AHF is a serious condition requiring urgent medical attention, which presents as a rapid onset of appropriate signs and symptoms, such as reduced cardiac output, decreased tissue perfusion and increased pulmonary and/or peripheral congestion, with or without previously known cardiac disease. Common presenting symptoms include shortness of breath on minimal effort or when lying down, cough, increasing abdominal girth, edema and fatigue. This clinical syndrome is attributed to systolic or diastolic myocardial dysfunction, valvular dysfunction or cardiac rhythm abnormalities, but may have the following clinical presentations: 'de novo'; decompensation of known chronic heart failure; hypertension; pulmonary edema; cardiogenic shock; high-output failure (anemia, thyrotoxicosis, arrhythmias and Paget's disease); or predominant right heart failure with increased jugular venous pressure, peripheral edema or ascites. The Acute Decompensated Heart Failure National Registry (ADHERE), an acute decompensated heart failure national registry from the United States, reported that at presentation, 89% of patients had dyspnea, 68% had rales and 66% had peripheral edema. Only 2% of patients had a systolic BP lower than 90 mmHg (140).

Initial clinical evaluation
Recommendations:
- A thorough clinical evaluation of the AHF patient should include assessment of perfusion and volume status – cold or warm, wet or dry (class IIa, level C).
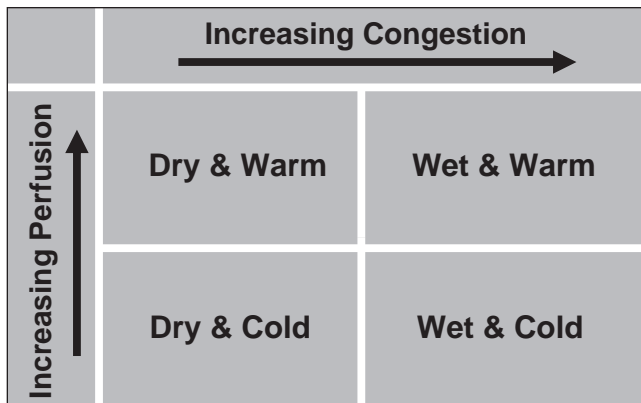
Figure 2) *Initial bedside assessment of perfusion and volume status in acute heart failure. Data from reference 141*

- Initial investigations should include testing serum creatinine and electrolyte levels, troponin measurements, complete blood count, ECG, chest x-ray and an echocardiogram if no recent echocardiogram is available (class I, level C).

- A precipitating cause should to be sought in all patients presenting with AHF (class I, level C).

A clinical assessment is based on a thorough and systematic history and physical examination for clinical findings related to peripheral temperature and vasoconstriction/perfusion, as well as assessment of congestion in the lungs, liver and extremities. The patients may be classifed as Group A (warm and dry), Group B (warm and wet), Group C (cold and wet) and Group D (cold and dry). Warm refers to well-perfused peripheries, whereas cold suggests that the peripheries are not adequately perfused (Figure 2) (141). Wet refers to congestion, whereas dry refers to no congestion. These profiles predict outcome, and should be used to guide investigation and therapy; these appear to be an excellent tool for assessing the patient with chronic heart failure who presents with an acute decompensation (141).

Vital signs may reveal an increased respiratory rate and resting heart rate, although BP may be low, normal or high. The jugular venous pressure is useful to assess right ventricular (RV) filling, and in RV congestion, hepatomegaly may be present. Evaluation of LV filling pressures is difficult, but clues to increased LV end-diastolic pressure include rales and crackles on pulmonary auscultation. Cardiac examination may reveal tachycardia, irregular rhythm, murmurs or extra heart sounds (third and fourth heart sounds). Peripheral examination will reveal the level of perfusion and congestion, but may also detect the presence of atherosclerosis, with diminished or absent pulses or the presence of bruits.

Although the diagnosis of AHF is based on clinical signs and symptoms, it should be confirmed by additional tests that may point to etiology and precipitating factors. Serum electrolytes, renal function (BUN and creatinine levels), troponin level and complete blood count are mandatory tests, and should be done at initial presentation. In addition, albumin, D-dimer, liver and thyroid function tests may be useful in selected patients. Arterial blood gas analysis may help in the assessment of oxygenation (partial pressure of oxygen), respiratory efficacy (partial pressure of carbon dioxide), acid-base metabolism (pH and lactate level) and should be performed in all patients who are vasoconstricted or in cardiogenic shock. Otherwise, pulse oximetry is an adequate alternative.

Plasma BNP is released from the cardiac ventricles in response to increased wall stretch or volume overload, and has been extensively used for diagnosis and prognosis in patients with AHF. BNP is discussed in more detail later under the 'Biomarkers' section. Its use in excluding ('ruling out' and/or recognizing heart failure) in patients admitted to the emergency department for dyspnea is well established (142,143). A BNP concentration lower than 100 pg/mL or an NT-proBNP concentration lower than 300 pg/mL indicates a low probability of AHF. Conversely, a BNP concentration greater than 500 pg/mL or an NT-proBNP concentration greater than 900 pg/mL indicates a very high probability of AHF and carries prognostic information (for concentrations greater than 450 pg/mL in patients younger than 50 years of age or concentrations greater than 1800 pg/mL in patients older than 75 years of age, see the 'Biomarkers' section). However, in AHF of very rapid onset ('flash' pulmonary edema), BNP levels may be normal at the time of first presentation. Otherwise, BNP levels have a good negative predictive value in excluding heart failure (144). Clinical conditions that may affect BNP levels include renal failure and sepsis, which may raise BNP levels, and obesity, which may lower BNP levels. The role of BNP levels in non-AHF and community outpatient practice remains to be fully clarified (145).

It is essential to perform an ECG in AHF, even though it may sometimes be normal. It assists in identifying rhythm abnormalities (atrial fibrillation, flutter or bradycardia and ventricular tachycardias), acute coronary syndromes (146), RV, LV or atrial hypertrophy or strain, as well as myopericarditis. Cardiac arrhythmias should be evaluated by a 12-lead ECG and continuous ECG monitoring. A chest x-ray should also be performed in all patients with suspected AHF within the first 1 h to 2 h of arrival to assess cardiac size and shape, pulmonary congestion and other pulmonary conditions. It is important for confirmation of the diagnosis, and may also be useful during follow-up for evidence of improvement or unsatisfactory response to therapy. In some cases, a thoracic computed tomography scan with or without contrast agent or ventilation-perfusion scintigraphy may help when pulmonary embolism or another pulmonary disease is suspected as the cause of AHF. Echocardiography with Doppler imaging is an essential tool in evaluating global and regional LV and RV function and geometry, LV diastolic function, valvular disease, pulmonary artery pressures, cardiac index, mechanical complications of acute coronary syndromes and disease of the pericardium (147). In cases in which AHF is considered secondary to an acute or recent coronary syndrome, coronary angiography should be considered because appropriate revascularization has been shown to improve prognosis (146).

Patients presenting with AHF should be questioned about potential etiology and precipitating factors (Table 1 [see page 24]). In the vast majority of cases (75% to 80%) (148,149), an offender can be found. Failure to uncover the responsible precipitating factor may lead to intractable heart failure. Noncompliance with diet or medication intake, as well as infections, arrhythmias, pulmonary embolism and acute coronary syndrome, are frequent situations that may cause AHF.

Initial management approach for AHF
Recommendations

- Heart rate, BP and oxygen saturation should be measured frequently until the patient is stabilized (class IIa, level C).

- All patients with AHF should have careful monitoring of fluid balance, including urine output, and this may require bladder catheterization (class I, level C).

- If the patient is in shock or has significant renal dysfunction, laboratory tests, particularly for serum electrolytes and renal function, should be checked regularly in the first 24 h of presentation (class I, level C).

- Invasive monitoring with arterial lines or central venous pressure lines may be necessary for patients in cardiogenic shock or for those who require pressors (class II b, level C).

Monitoring should be initiated as soon as possible, along with diagnostic procedures directed toward the underlying etiology. The extent of surveillance and monitoring required for a particular patient will depend on the severity of the illness and the response to initial therapy. Immediate therapy is directed toward hemodynamic stabilization, adequate oxygen delivery to the tissue, as well as symptom improvement (150,151). To reach these goals, AHF patients should be treated without delay by staff with skills in AHF management (152). Diagnostic (echocardiography) and therapeutic procedures (coronary percutaneous intervention or cardioversion for a persistent arrhythmia) should be available in a timely manner.

Vital sign measurements should be made on a regular basis until stabilization of BP and oxygenation. Several laboratory tests have to be repeated regularly (at least daily in the first two to three days): electrolytes, BUN, creatinine and complete blood count if abnormal. Electrolyte abnormalities should be prevented (eg, by potassium supplementation with diuretics) or corrected promptly if they do occur. Patients with significant renal impairment may require more frequent laboratory tests to monitor renal function and electrolytes. A close interrelationship exists between AHF and renal failure, and both may cause, aggravate and influence each other.

If the patient's clinical status deteriorates despite initial therapy, closer supervision, such as transfer to an intensive care unit, is warranted. Patients with AHF who are in cardiogenic shock or those who have difficulty voiding should have a bladder catheter to monitor urinary output monitoring. The decision to insert an arterial line (usually radial) depends on the need for either continuous analysis of BP due to hemodynamic instability with low BP or the requirement for repeated arterial blood analyses. A central intravenous line depends on the need for either delivery of fluids and drugs or for monitoring central venous pressure and venous oxygen saturation, which provides an estimate of oxygen transport. However, in critically ill patients with AHF, right atrial pressure does not correlate well with left atrial and LV filling pressures. The insertion of a pulmonary artery catheter is not usually necessary for the diagnosis of AHF. It may, however, be useful in some patients to distinguish between cardiogenic and noncardiogenic shock, to guide therapy in the presence of severe diffuse pulmonary disease or in hemodynamically unstable patients who do not respond in a predictable fashion to the initial therapy (153).

Medical treatment of AHF
Recommendations

- Any identified precipitating cause should be promptly corrected when possible (eg, cardioversion for a tachyarrhythmia) (class I, level B).

- Oxygen should be given initially to all patients presenting with AHF and hypoxia (class I, level C).

- Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP) or endotracheal intubation should be considered if hypoxemia persists despite increasing incremental fraction of oxygen (class IIa, level B).

- Intravenous diuretics should be given as first-line therapy for patients with AHF and congestion (class I, level B).

- Vasodilators should be considered for patients with dyspnea at rest (class I, level C).

- Positive inotropes should be reserved for patients in cardiogenic shock and/or volume overload with diuretic resistance. They should be used for short-term therapy to stabilize the patient. In hypotensive patients (systolic BP of 90 mmHg), dobutamine is preferred over milrinone (class I, level C).

- ACE inhibitors are not recommended routinely in the first few hours of AHF. They should be introduced when the patient is stabilized (class I, level B).

- Calcium channel blockers are not recommended in AHF; specifically, diltiazem and verapamil are to be avoided in AHF with systolic dysfunction (class III, level B).

- Diltiazem may be used in AHF with preserved systolic function in the setting of atrial fibrillation with rapid ventricular response (class I, level C).

- For patients with refractory heart failure despite medical therapy, an intra-aortic balloon pump (IABP) may be considered (class IIb, level B).

- Patients who remain in cardiogenic shock and have a low comorbid burden should be transferred early to a tertiary care centre in which circulatory mechanical support and transplantation are available (class I, level C).

Adequate oxygen delivery to the tissues (systemic arterial oxygen saturation of 95%) is important to help prevent tissue hypoxia and multiple organ failure. This first implies a patent airway with administration of incremental fraction of oxygen. BIPAP or CPAP should be considered for patients with a high respiratory rate (more than 25 breaths/min), and who are breathing with great effort and use of accessory muscles, or have

persistent systemic arterial hypoxia despite high flow oxygen administration. Endotracheal intubation may be warranted if these less invasive modes of oxygen delivery fail to improve tissue oxygenation or if the patient is cardiogenic shock.

Despite their broad acceptance, there are no outcome data derived from randomized clinical trials of the use of intravenous diuretics in AHF. However, intravenous diuretics increase urine output by excretion of sodium and water, leading to a decrease in plasma and extracellular fluid volume, total body water and sodium, a reduction in RV and LV filling pressures, as well as a decrease in peripheral congestion and pulmonary edema (154,155). Intravenous loop diuretics also cause an early (5 min to 30 min) decrease in right atrial and pulmonary wedge pressure through a vasodilatory effect (156). When using high intravenous doses (0.1 mg/kg), reflex vasoconstriction may occur. In AHF, by normalizing loading conditions, these high doses may reduce neurohormonal activation in the short term (157). Patients presenting with AHF and congestion should receive intravenous loop diuretics (furosemide, bumetanide or torasemide). Therapy may be initiated in the ambulance (158), heart failure clinic (159) or in hospital, and doses should be adjusted according to diuresis and clinical response (improved symptoms of shortness of breath and improved oxygenation). A combination of diuretics with thiazides (159-161) or spironolactone (162) has been proposed and seems to be effective, with fewer side effects than a higher dose of a loop diuretic. In patients with severe right heart failure, oral diuretics may not be adequately absorbed and may therefore be of little use. Dobutamine, milrinone, dopamine or nitrates (92,163) may also be used in combination with loop diuretics to promote diuresis while reducing side effects. This strategy may also be helpful in preventing diuretic resistance.

There are limited data and randomized control trial information available regarding the use of positive inotropes or vasodilators for the treatment of AHF. The ADHERE registry of 65,180 patients with AHF from 263 hospitals showed that only 1% of AHF patients with preserved LVEF and 4% of AHF with reduced LVEF have a systolic BP of 90 mmHg or lower (164). However, positive inotropes (dobutamine, milrinone or dopamine) were used in 8% of patients with preserved LVEF and in 19% of patients with reduced LVEF. Vasodilators (nesiritide, nitroglycerin or nitroprusside) were used in 18% of patients with preserved LVEF and in 24% of patients with reduced LVEF and AHF; 16% of patients received more than one vasoactive therapy, which was associated with a longer length of intensive care unit or coronary care unit and hospital stay (165). Risk factors for increased mortality included BUN levels greater than 42 mg/dL (10.5 mmol/L) (OR 3.34), systolic BP of 115 mmHg or lower (OR 3.09), diastolic BP of 55 mmHg or lower (OR 2.87), serum sodium level of 134 mmol/L or lower (OR 2.26), creatinine level greater than 3.2 mg/dL (283 μmol/L) (OR 1.99), age older than 78 years (OR 1.88), dyspnea at rest (OR 1.57) and heart rate of more than 84 beats/min (OR 1.20). For both adjusted and unadjusted OR, mortality was lower in patients treated with nitroglycerin or nesiritide versus dobutamine or milrinone. The unadjusted OR of mortality was higher in those treated with nesiritide versus nitroglycerin; however, the covariate and propensity score-adjusted OR was 0.94 in favour of nesiritide.

There is a need for further randomized controlled trials to assess treatment options in AHF with preserved and reduced LVEF, and in the setting of the hemodynamically stable patient. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF [166]) was a prospective, randomized, double-blind, placebo-controlled trial of 951 patients in 78 community and tertiary care hospitals in the United States. Patients (mean age 65 years, NYHA class III to IV in 92%, mean LVEF of 23%), admitted with an exacerbation of systolic heart failure that did not require intravenous inotropic support, were randomly assigned to a 48 h infusion of milrinone (0.5 μg/kg/min) versus saline placebo. New-onset atrial arrhythmias, worsening of heart failure and symptomatic hypotension requiring intervention occurred more frequently in the milrinone group. There was no difference in in-hospital mortality, or composite incidence of death or readmission at 60 days; however, a nonsignificant increase in the number of deaths in hospital and after 60 days was seen in the milrinone group. A posthoc analysis demonstrated a higher incidence of death or rehospitalization in patients with underlying ischemic etiology of heart failure (42% for milrinone versus 36% for placebo, P=0.01) (167). There are no placebo-controlled trials assessing dobutamine efficacy in AHF, but it is clearly associated with increased incidence of arrhythmias (168). Levosimendan, a calcium-sensitizing inodilator, has been reported to reduce mortality compared with dobutamine and placebo (169). In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy II (REVIVE-II) trial (169), levosimendan showed modest benefit over placebo, but there was more hypotension and atrial fibrillation, and mortality at 90 days was higher. In the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study (169), there was a trend to early benefit with levosimendan over dobutamine that was not evident past the period of hemodynamic efficacy of the drug; there was more atrial fibrillation, and mortality was comparable at the end of the study (169). Because there was no placebo-treated arm in this study, although levosimendan appeared to have better efficacy and safety than dobutamine, this is not to say that it is superior to placebo.

Much data on nitroglycerin are nonrandomized and somewhat dated. However, a recent study (163) showed that high-dose nitroglycerin was more effective than furosemide in controlling severe pulmonary edema. There are no randomized controlled trials assessing the safety and/or efficacy of nitroprusside in the treatment of AHF. The Vasodilator in the Management of Acute Heart Failure (VMAC) trial compared nesiritide (n=204), nitroglycerin (n=143) or placebo (n=142) added to standard therapy for 3 h, followed by nesiritide (n=278) or nitroglycerin (n=216) added to standard treatment for 24 h in AHF patients with dyspnea at rest. The study included a subset of 246 patients who received pulmonary artery catheterization. The primary end points of changes in pulmonary capillary wedge pressure and patient self-evaluation of dyspnea at 3 h were improved with nesiritide versus placebo. There was a significantly greater reduction in pulmonary capillary wedge pressure with nesiritide (–5.8 mmHg) versus nitroglycerin (–3.8 mmHg) at 3 h and 8 h (–8.2 mmHg versus –6.3 mmHg); however, there was no difference in dyspnea. Six-month mortality was similar (25.1% with nesiritide, 20.8% with nitroglycerin) (170). Since the VMAC trial, two meta-analyses pooled 12 randomized controlled trials evaluating nesiritide, three of which met all the inclusion criteria for the mortality assessment and five studies met the criteria for renal

dysfunction. The pooled results suggested an increased 30-day mortality with nesiritide (unadjusted HR 1.74, 95% CI 0.97 to 3.12, P=0.059; adjusted HR 1.80, 95% CI 0.98 to 3.31, P=0.057) (171,172). The RR of renal dysfunction with nesiritide across the studies was 1.52 (95% CI 1.16 to 2.00, P=0.003). Another retrospective review did not identify a significant safety concern (173). A large-scale trial prospective randomized trial of nesiritide in the treatment of AHF is currently planned to test safety and efficacy. Endothelin antagonists have been studied in the treatment of AHF, but a large randomized trial of tezosentan 1 mg/h versus placebo in 1400 AHF patients with dyspnea was stopped for futility without significant safety concerns (174-178).

Cardiogenic shock refractory to medical therapy

Three to five per cent of patients with AHF present in cardiogenic shock. A stepwise, graded approach to circulatory support based on the underlying cardiac pathology is required. Acute mechanical problems, such as acute mitral valve rupture or ventricular septal defect, may require surgical correction in appropriately selected patients. For patients who remain in cardiogenic shock, despite best treatments discussed above, timely institution of IABP may improve cardiac performance by increasing coronary artery perfusion and by assisting ventricular unloading. However, IABP support may augment cardiac output by only 10% to 15%. Contraindications to IABP support include descending thoracic or abdominal aortic disease and significant aortic insufficiency; the efficacy of IABP support is also questionable in young patients (younger than 40 years of age) who have very elastic and compliant aortas (179).

For patients who remain in profound, refractory cardiogenic shock, but are expected to recover and are thought to be potential transplant candidates, mechanical cardiac support should be considered; extracorporeal membrane oxygenation (ECMO) may initially be considered. This allows diversion of a patient's blood volume through an external circuit, which circulates the blood through an oxygenator and a heat exchanger before returning it to the patient. A dialysis membrane may also be added for renal replacement therapy. Despite the fact that ECMO may provide adequate perfusion and reverse metabolic acidosis, myocardial unloading is incomplete due to the absence of a compliance chamber and may, in turn, delay or impede recovery. In addition, the extended blood path of a typical ECMO circuit may damage circulating blood cells and activate inflammatory cascades, which may lead to multi-organ dysfunction. ECMO circuits require anticoagulation, and hemorrhagic complications are not uncommon. Although ECMO can be instituted rapidly and permit a timely evaluation of neurological status and transplant candidacy, prolonged support (more than four days) has been associated with poor survival. Early consideration should be given to conversion to a long-term ventricular assist device (VAD) in eligible candidates (180).

Advanced options for circulatory support include VAD technologies for a small subset of the sickest patients and are limited in availability because of cost and expertise. VADs typically allow complete unloading of the native heart. They are implanted in a paracorporeal position, in which the blood pump is external and the cannulae traverse the skin to enter the mediastinum, or in the intracorporeal position, in which patients are tethered by a percutaneous driveline connecting the device to a computer and battery pack providing 2 h to 8 h of autonomy on a single charge, depending on the device and the energy

demand. Rapid evolution in mechanical circulatory support technology has allowed the implementation of cardiac assist devices within clinical management algorithms for patients with end-stage heart disease or cardiogenic shock. As such, this standard of care presents opportunities and challenges for all those involved in the care of this complex population (181).

The hub-and-spoke paradigm for mechanical cardiac assist has been developed with a view to extending mechanical circulatory support services to a broad geographic-based population, in a highly structured, organized network of nontransplant cardiac centres (spokes) collaborating with an identified multidisciplinary heart failure/mechanical assist/transplant program (hub). In keeping with this model, hub-centre and spoke-centre partnerships espousing this joint management philosophy, would, once established, agree on indications for patient entry into this clinical pathway, and appropriate technological and training resources would be shared. Successful implementation of such a program would be based on early and effective communication between centres, agreeing on device selection and management, patient stabilization strategies, and preparation and mechanisms for transport to a hub centre (182).

Practical tips:
- Vasodilators, including nitroglycerin (sublingual or intravenous), oral nitrates, intravenous nitroprusside and nesiritide (when available), may be useful in the initial management of AHF with systolic BP greater than 100 mmHg.

- Patients who remain in cardiogenic shock but are expected to recover with further support or are heart transplant candidates should be considered for ECMO and VAD support.

BIOMARKERS IN HEART FAILURE
Recommendations
- BNP/NT-proBNP levels should be measured to help confirm or rule out a diagnosis of heart failure in the acute or ambulatory care setting in patients in whom the clinical diagnosis is in doubt (class I, level A).

- Measurement of BNP/NT-proBNP levels may be considered in patients with an established diagnosis of heart failure for prognostic stratification (class IIa, level A).

- Sequential measurements of BNP/NT-proBNP levels may be considered to guide the therapy of patients with heart failure (class IIb, level B).

The term 'biomarker' was first introduced in the late 1980s as a medical subject heading term: "measurable and quantifiable biological parameters...which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, etc" (183). In 2001, a National Institute of Health working group standardized the definition as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic

intervention", and went on to define types of biomarkers (184). The expectation from a cardiac biomarker is that it can enhance clinicians' abilities to optimally manage patients with a cardiac disorder. Indeed, some of the most exciting discoveries in cardiology in the past two decades have been the development of biomarkers. Blood assays have been developed for several markers that can be used as adjuncts in primary prevention and screening, as well as in diagnostic, prognostic and therapeutic strategies for a variety of CV diseases and their related clinical events.

Biomarkers in heart failure

One good example of the application of biomarkers is in the management of heart failure. The diagnosis of heart failure is usually based on history, physical examination, chest radiography and, if available, LV function assessment. However, in many instances, diagnosing heart failure based on conventional subjective measures may be very difficult (185). Furthermore, LV function assessment may not be readily available, particularly in the urgent care settings. Patients with heart failure and preserved systolic LV function may have unremarkable echocardiographic findings (186,187). Indeed, many studies have now demonstrated that diagnosis of heart failure based on clinical assessment and standard testing may be inadequate (188-190). For these reasons, there has been a great effort to develop biomarkers that would offer incremental value to conventional clinical tools to establish rapid and accurate diagnosis and risk stratification of patients with heart failure.

The natriuretic peptides

To date, the only biomarker that has been developed for clinical use in heart failure is the group of natriuretic peptides. The natriuretic peptide family consists of the atrial natriuretic peptide, BNP and three other structurally similar peptides: C-type natriuretic peptide, which is mostly of central nervous system and endothelial origin; urodilatin from the kidney; and dendroaspis natriuretic peptide, which is of unknown significance at present (191-193). Among the natriuretic peptides, BNP and the amino-terminal fragment of the prohormone (NT-proBNP) have been at the most advanced stage of development for clinical use (193).

BNP and NT-proBNP as diagnostic markers in heart failure

Ample evidence exists attesting the use of BNP as a diagnostic marker to rule in and rule out heart failure in patients presenting to emergency departments with dyspnea. The development of a fluorescence immunoassay allowed for the point-of-care determination of BNP in whole blood and plasma. The largest study of the diagnostic utility of BNP is the Breathing Not Properly (BNP) Multinational Study (143,191). In this multicentre study, 1586 patients presenting to emergency departments with dyspnea had BNP levels determined using the rapid assay. Diagnosis of heart failure was adjudicated by cardiologists blinded to the BNP level results. BNP level was more accurate than clinical evaluation in identifying heart failure as the cause of dyspnea. Using a cut-off point of 100 pg/mL, the diagnostic accuracy was 83%. Similarly favourable results have been demonstrated with the use of the laboratory-based NT-proBNP assay (194,195). In the single-institution N-terminal Pro-BNP Investigation of Dyspnea in the Emergency

department (PRIDE) study (195), 600 patients presenting to an emergency department with dyspnea were prospectively evaluated. NT-proBNP levels at cut-off points greater than 450 pg/mL for patients younger than 50 years of age and more than 900 pg/mLfor patients 50 years of age and older were both sensitive and specific for the diagnosis of heart failure. An NT-proBNP level lower than 300 pg/mL was optimal for ruling out heart failure, with a negative predictive value of 99% regardless of age. Equally favourable results were observed in Canadian urgent care settings from the recently presented Canadian multicentre Improved Management of Congestive Heart Failure (IMPROVE-CHF) trial (Figure 3). Other than in acute settings, several studies have also established the value of NT-proBNP levels in the diagnosis of heart failure in an outpatient setting (196-198). A potentially useful application of BNP levels is for the diagnosis of heart failure in patients with heart failure and preserved LVEF. By definition, these patients have normal LVEF, and therefore, heart failure cannot be easily diagnosed by an assessment of LV systolic function. BNP level is elevated in patients with heart failure or diastolic dysfunction based on Doppler filling characteristics (199). The area under the receiver-operating-characteristics curve to detect diastolic dysfunction in patients with heart failure with preserved LVEF was 0.96 using a traditional radioimmunoassay (200), and 0.92 in patients with or without symptoms using a commercial rapid assay (201). Although BNP level in heart failure in patients with preserved LVEF tends to be lower than that in patients with heart failure and systolic dysfunction, BNP level by itself cannot be used to differentiate between systolic and diastolic dysfunction.

BNP level can increase in conditions other than heart failure. Indeed, plasma BNP and NT-proBNP levels increase with age, as well as in women, patients with renal failure, pulmonary disease, malignancy, beta blockade therapy and in any conditions that increase load to the cardiac ventricles (202). On the other hand, BNP level may be falsely low in obese individuals and in patients with flash pulmonary edema; in the latter case, there is not enough time for the ventricles to produce and release BNP to increase the circulating level (202-204). However, secondary reports of the BNP and PRIDE studies have shown preserved diagnostic use of BNP and NT-proBNP in the presence of renal failure, although the cut-off points have to be adjusted (205,206).

In summary, BNP/NT-proBNP testing is useful and complementary to clinical evaluations in diagnosing heart failure. The test is most useful in patients whose history, physical examination and chest radiographs are suggestive, but not clearly diagnostic of heart failure. In practice, in patients presenting with dyspnea and a BNP level measured from the point-of-care assay lower than 100 pg/mL or NT-proBNP level lower than 300 pg/mL, a diagnosis of heart failure is likely ruled out. For those with BNP levels 100 pg/mL to 500 pg/mL or NT-proBNP levels 300 pg/mL to 450 pg/mL in those younger than 50 years of age, or 300 pg/mL to 900 pg/mL in those 50 to 75 years of age, a diagnosis of heart failure is possible, but other diagnoses such as chronic LV dysfunction, lung disease or pulmonary embolism should be considered. For patients with BNP levels less than 500 pg/mL and NT-proBNP levels greater than 450 pg/mL in those younger than 50 years of age, levels greater than 900 pg/mL in those 50 to 75 years of age and levels greater than 1800 pg/mL in those older than 75 years of age, heart failure is very likely. Appropriate BNP levels that may be
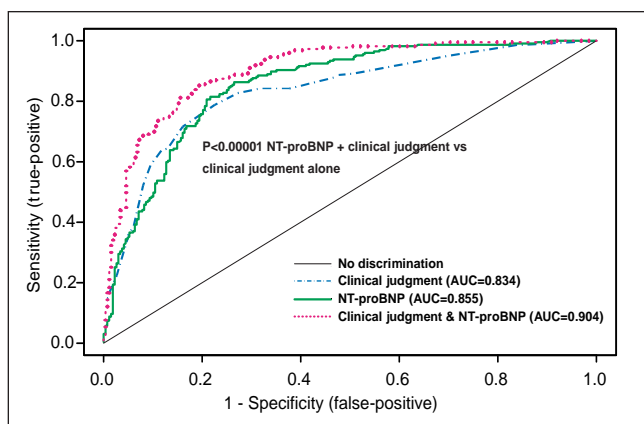
Figure 3) *Receiver-operating characteristics curves for clinical judgment alone, prohormone of brain natriuretic peptide (NT-proBNP) and combined NT-proBNP and clinical judgment in the Canadian Improved Management of Congestive Heart Failure (IMPROVE-CHF) study. AUC Area under the curve*

TABLE 3
Brain natriuretic peptide (BNP) and prohormone of BNP (NT-proBNP) assay cut-off points for the diagnosis of heart failure

	Age (years)	Heart failure is unlikely	Heart failure is possible, but other diagnoses need to be considered	Heart failure is very likely
BNP*	All	<100 pg/mL	100 pg/mL – 500 pg/mL	>500 pg/mL
NT-proBNP	<50	<300 pg/mL	300 pg/mL – 450 pg/mL	>450 pg/mL
	50–75	<300 pg/mL	450 pg/mL – 900 pg/mL	>900 pg/mL
	>75	<300 pg/mL	900 pg/mL – 1800 pg/mL	>1800 pg/mL

Point-of-care assay

used as clinical cut-off points for diagnosis and management are given in Table 3.

BNP as a prognostic marker in heart failure

BNP and NT-proBNP levels correlate with the severity of heart failure (207-209). A large body of evidence exists confirming BNP and/or NT-proBNP as independent predictors of total mortality, CV mortality and heart failure hospitalization in both acute and chronic heart failure (210-218). In patients presenting to the emergency department with dyspnea, BNP levels measured at the time of presentation were highly predictive of cardiac events over the next six months (214). A BNP value of 480 pg/mL had a sensitivity of 68%, a specificity of 88% and an accuracy of 85% for predicting a subsequent heart failure end point. Patients with BNP levels greater than 480 pg/mL had a 51% six-month cumulative probability of a heart failure event, whereas those with BNP levels less than 230 pg/mL had an excellent prognosis, with only a 2.5% incidence of heart failure end points. In a prospective evaluation of 142 consecutive patients with advanced heart failure referred for cardiac transplantation (217), an NT-proBNP level above the median was the only independent predictor of mortality and combined mortality and urgent transplantation. The Rapid Emergency Department Heart failure Outpatient Trial (REDHOT) examined the relationships between BNP levels, perceived heart failure severity, clinical decision-making and outcomes of patients presenting to emergency department with dyspnea (218); patients were followed up for 90 days. Of the 464 patients, 90% were hospitalized. Two-thirds of patients were perceived to be at NYHA functional class III or IV. BNP levels did not differ between patients who were discharged and those admitted. Emergency physicians' intentions to admit or discharge patients had no influence on 90-day outcomes, although BNP level was a strong predictor of outcome. Of the admitted patients, 11% had BNP levels less than 200 pg/mL (66% of which were perceived NYHA functional class III or IV). The 90-day combined event rate (heart failure visits/admissions and mortality) in the group of patients admitted with BNP levels less than 200 pg/mL and greater than 200 pg/mL was 9% and 29%, respectively (P=0.006). In a one-year follow-up of patients in the PRIDE study (219),

NT-proBNP concentrations obtained from the emergency department were found to predict one-year mortality, with an optimal cut-off point of 986 pg/mL, regardless of whether the patients had a diagnosis of heart failure.

In summary, BNP and NT-proBNP are strong, independent predictors of adverse clinical outcomes in a variety of patient populations, including those with heart failure. This prognostic use of this biomarker could potentially aid clinicians in their decision-making and management of heart failure patients.

The impact of a knowledge of BNP/NT-proBNP level results on the management of heart failure

There is increasing evidence to support the concept that the provision of knowledge of plasma BNP levels may be translated to improved management in the form of improved clinical outcomes and cost savings. Data are still being accumulated because several randomized controlled trials are either ongoing or just being completed.

A pilot study by Troughton et al (220) was the first attempt to evaluate such an approach. In the study, 69 patients with decompensated heart failure were randomly assigned to have therapy adjusted according to a preset clinical algorithm or to serial plasma levels of NT-proBNP. In the BNP-guided group, NT-proBNP levels above 200 pmol/L (approximately 1700 pg/mL) triggered intensification of therapy even when the clinical threshold was not exceeded. At 9.5 months' follow-up, clinical outcomes were significantly improved in the BNP-guided group. Nineteen adverse CV events in the NT-proBNP-guided group compared favourably with 54 events in the clinically managed patients (P=0.02). Although the data were promising, the sample size of the study was small and the study was conducted in an era before contemporary heart failure therapy. In the multicentre Systolic heart failure Treatment Supported by BNP (STARS-BNP) randomized trial (221), which is still in abstract form, 220 patients with heart failure were randomly assigned to BNP versus clinically guided treatment. In a median follow-up period of 15 months, there were significantly fewer events – death or heart failure hospitalization – in the BNP group than in the clinical group.

There are now randomized, controlled data to show that the use of BNP/NT-proBNP levels is also associated with cost savings in the management of patients presenting to emergency departments with dyspnea. In the Acute Shortness of

Breath Evaluation (BASEL) study of patients presenting to a single emergency department with dyspnea, 225 were randomly assigned to a strategy involving the measurement of BNP levels with the bedside assay, and 227 were assessed in a standard manner. The use of BNP levels reduced the need for hospitalization and intensive care. A cost reduction of 26% over a 30-day period and 25% over 180 days were reported (222,223). In the Canadian multicentre IMPROVE-CHF study 244 patients were randomly assigned to NT-proBNP-guided management and 251 to usual care. Knowledge of NT-proBNP results reduced the direct medical costs, including initial and subsequent emergency department visits, hospitalizations and outpatient services from $7405 to $6310 (P=0.017). In addition, the duration of the emergency department visit (6.3 h to 5.6 h, P=0.038) and the number of patients rehospitalized (51 to 33, P=0.044) were reduced (197).

Although sequential changes of BNP and NT-proBNP levels over time correlate with treatment response and clinical outcome (208,224), it is still unproven whether using a treatment approach that is guided by BNP or NT-proBNP values would result in improved clinical outcomes. One such ongoing trial is evaluating management of heart failure based on knowledge of NT-proBNP levels (the BNP-Assisted Treatment To LEssen Serial CARdiac REadmissions and Death [BATTLE-SCARRED] trial).

Other biomarkers and prognostic markers

Other biomarkers that have been evaluated in patients with heart failure include the cardiac troponins. Although elevated troponin I and troponin T levels have been reported in patients with heart failure and have been shown to be associated with adverse clinical outcomes (225-229), these studies have typically involved relatively small numbers of patients. Furthermore, the sensitivity and specificity of cardiac troponins, as well as the optimal cut-off points for diagnosis and prognosis in heart failure, have not been properly defined. Finally, it is also unclear whether troponin results provide any information that is independent or incremental to those of BNP/NT-proBNP levels.

There are other circulating markers of underlying pathololological mechanisms operative in patients with heart failure that are not usually classified as biomarkers, but could be used as prognostic markers in these patients. These include simple demographic parameters, such as age and BP (230,231), measures of impaired renal function (232) and anemia, (233-235), as well as neurohormones, including noradrenaline, angiotensin II, arginine vasopressin and endothelin-1, which are not usually available for clinical use (236), but elevations of all of these parameters are related to prognosis in patients with heart failure.

Summary and conclusions

The clinical use of the BNP and NT-proBNP levels as biomarkers in heart failure has been thoroughly evaluated. Indeed, the use of natriuretic peptides as an aid to diagnose heart failure has now been endorsed in several heart failure consensus guidelines, including the 2006 CCS Heart Failure Consensus Conference (236-239).

Practical tips:
• The use such biomarkers as BNP and NT-proBNP levels should be complementary to, but not replace, good clinical evaluation.

• There are no compelling factors that favour the use of the BNP versus the NT-proBNP assay. The choice is dictated by availability as well as the clinician's familiarity, particularly with respect to interpretation.

• To rule out or rule in a diagnosis of heart failure in patients presenting to emergency departments with dyspnea and suspected heart failure, cut-off points of the two assays are given in Table 3.

• In patients with BNP levels (point-of-care assay) less than 100 pg/mL or NT-proBNP level less than 300 pg/mL, a diagnosis of heart failure is very unlikely. In patients with BNP levels of 100 pg/mL to 500 pg/mL, or NT-proBNP levels of 300 pg/mL to 450 pg/mL in those younger than 50 years of age and 300 pg/mL to 900 pg/mL in those 50 to 75 years of age, a diagnosis of heart failure is possible, but other diagnoses such as chronic LV dysfunction, lung disease or pulmonary embolism should be considered. For patients with BNP levels greater than 500 pg/mL and NT-proBNP levels greater than 450 pg/mL in those younger than 50 years of age, greater than 900 pg/mL in those 50 to 75 years of age and greater than 1800 pg/mL in those older than 75 years of age, a diagnosis of heart failure is very likely.

WHAT IS ON THE HORIZON?

Our understanding of heart failure has grown exponentially over the past 20 years and has fuelled many landmark clinical trials that have given definitive answers. The recommendations in the present paper are based on clinical trials that have already been conducted. Fortunately, there are many trials that are currently in progress or planning. These cover all aspects, from innovative drugs and devices to new applications of current drugs, and health care research. They will provide new information and evidence to guide future recommendations and guidelines. Although it is not possible to list all such trials, Table 4 presents some that cover the range of exciting new areas of research, many of which involve centres in Canada.

CONCLUSIONS

The practice of medicine requires knowledge, experience, good judgment and compassion. Well-designed clinical trials may provide evidence-based treatment choices and algorithms for care, but physicians and other health care providers are also informed by peers they respect and by their own experience. The current recommendations and practical tips will provide advice and help in several challenging areas of heart failure management. The treatment recommendations from 2006 have been combined with those for prevention from 2007 to provide a summary algorithm of the approach to a patient (Figure 4), as well as the drugs and doses studied in landmark clinical trials (Table 5). Knowing how to recognize the problems and the appropriate options will result in improved care and outcomes. Dissemination of these recommendations will occur when they are published, but it will also depend on planned interactive educational workshops and the example of health care professionals who put the recommendations into practice. Tools are being developed to help in this process, but local opinion leaders will be critical to teach in local communities. If physicians and other health

TABLE 4
New and ongoing trials in heart failure*

Exercise prescription
- HF-ACTION

Atrial fibrillation
- AF-CHF (rate versus rhythm control)

Anticoagulation
- WARCEF (warfarin versus acetylsalicylic acid)

Anemia
- RED-HF (erythropoietin)

Diastolic heart failure
- I-PRESERVE (irbesartan), TOPCAT (spironolactone)

Acute heart failure
- UNLOAD (ultrafiltration)
- ASCEND-HF (nesiritide)
- REVIVE (levosimendan versus placebo), SURVIVE (levosimendan versus dobutamine)

Vasopressin antagonist
- EVEREST (tolvaptan)

Ischemic heart disease
- STICH (Surgical remodelling/revascularization versus medical therapy)

Devices
- RAFT, REVERSE, MADIT-CRT (all cardiac resynchronization therapies)

*List is not exhaustive and provides examples only. AF-CHF Atrial Fibrillation in Congestive Heart Failure; ASCEND-HF Acute Study of Clinical Effectiveness of Nesiritide in. Decompensated Heart Failure; EVEREST Efficacy of Vasopressin Antagonism in hEart failuRE: Outcome Study With Tolvaptan; HF-ACTION Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing; I-PRESERVE Irbesartan in heart failure with PRESERVEd systolic function; MADIT-CRT Multicenter Automatic Defibrillator Implantation Cardiac Resynchronization Therapy Trial; RAFT Resynchronization/defibrillation for Advanced Heart Failure Trial; RED-HF Reduction of Events with Darbepoetin alfa in Heart Failure; REVERSE REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction; REVIVE Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy; STICH Surgical Treatment for Ischemic Heart Failure; SURVIVE Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; TOPCAT Trial of Aldosterone Antagonist Therapy in Adults With Preserved Ejection Fraction Congestive Heart Failure; UNLOAD Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease; WARCEF Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction

care providers who are involved in the care of patients with heart failure are informed by the evidence and consensus opinion of experts, measurable improvements in health care outcomes can be achieved.

It is recognized that barriers to implementation exist, because heart failure patients are treated in a variety of circumstances by physicians with differing training and in health care systems that may not provide sufficient resources. While we have blood tests that may help to diagnose heart failure more accurately, the tests are not available in all communities. AHF is often misdiagnosed, resulting in delays in treatment. Hospital lengths of stay may be prolonged when heart failure is precipitated or aggravated by other intercurrent illnesses. Early identification of those at risk may not occur because of competing pressures on time in a busy office practice. The goal of the present recommendations is to improve heart failure outcomes, but this will also require a national health care strategy for heart failure with adequate funding to help prevent and
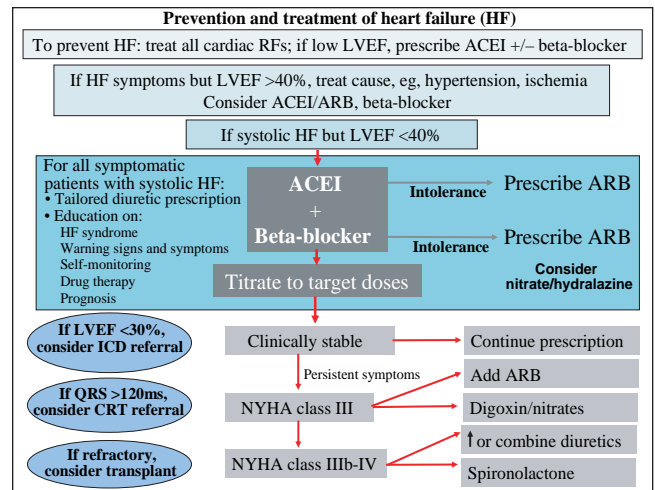

Figure 4) *Algorithm of the prevention and treatment of heart failure. ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; CRT Cardiac resynchronization therapy; ICD Implantable cardioverter defibrillator; LVEF Left ventricular ejection fraction; NYHA New York Heart Association; RF Risk factors*

TABLE 5
Evidence-based drugs and oral doses as used in large clinical trials for prevention and treatment of heart failure

Drug	Start dose	Target dose
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg – 12.5 mg tid	25 mg – 50 mg tid
Enalapril	1.25 mg – 2.5 mg bid	10 mg bid
Lisinopril	2.5 mg – 5 mg od	20 mg – 35 mg od
Perindopril	2 mg	8 mg
Ramipril	1.25 mg – 2.5 mg bid	5 mg bid*
Trandolopril	1 mg	4 mg
Beta-blockers		
Bisoprolol	1.25 mg od	10 mg od
Carvedilol	3.125 mg bid	25 mg bid
Metoprolol CR/XL†	12.5 mg – 25 mg od	200 mg od
Angiotensin receptor blockers		
Candesartan	4 mg od	32 mg od
Valsartan	40 mg bid	160 mg bid
Aldosterone antagonists		
Spironolactone	12.5 mg od	50 mg od
Eplerenone†	25 mg od	50 mg od
Vasodilators		
Hydralazine	37.5 mg tid	75 mg tid
Isorbide dinitrate	20 mg tid	40 mg tid

*The Healing and Early Afterload Reducing Therapy (HEART) trial (239) showed that 10 mg once a day (od) was effective to attenuate left ventricular remodelling. †Not available in Canada. bid Twice a day; CR/XL Controlled release/extended release; tid Three times a day

treat heart failure, which is a current health care epidemic, especially in the elderly.

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The following Primary Panel members also represented their respective societies: Ross Tsuyuki, Canadian Pharmacy Association; Anna Svendsen, Canadian Association of Cardiovascular Nurses; George Heckman, Canadian Geriatrics Society; Errol J Sequeira, Canadian College of Family Practitioners; Elizabeth Mann, Canadian Society of Internal Medicine; Kelly O'Halloran, Canadian Association of Advanced Practice Nurses.

CONFLICT OF INTEREST: The panelists had complete editorial independence in the development and writing of this manuscript, and functioned on a pro bono basis. A full description of the planning of this consensus conference and the ongoing process (including the needs assessment, the methods of searching for and selecting the evidence for review; the conflict of interest statements of panel members is available at <www.ccs.ca>.

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