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Society Guidelines

The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: Anemia, Biomarkers, and Recent Therapeutic Trial Implications

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The disclosure information of the authors and reviewers is available from the CCS website: www.ccs.ca.

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

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ABSTRACT

The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Update provides discussion on the management recommendations on 3 focused areas: (1) anemia; (2) biomarkers, especially natriuretic peptides; and (3) clinical trials that might change practice in the management of patients with heart failure. First, all patients with heart failure and anemia should be investigated for reversible causes of anemia. Second, patients with chronic stable heart failure should undergo natriuretic peptide testing. Third, considerations should be given to treat selected patients with heart failure and preserved systolic function with a mineralocorticoid receptor antagonist and to treat patients with heart failure and reduced ejection fraction with an angiotensin receptor/neprilysin inhibitor, when the drug is approved. As with updates in previous years, the topics were chosen in response to stakeholder feedback. The 2014 Update includes recommendations, values and preferences, and practical tips to assist the clinicians and health care workers to best manage patients with heart failure.

RÉSUMÉ

La mise à jour 2014 des Lignes directrices de la Societe canadienne de cardiologie sur la prise en charge de l'insuffisance cardiaque aborde les recommandations de prise en charge de 3 domaines spécialisés : 1) l'anémie; 2) les biomarqueurs, particulièrement les peptides natriurétiques; 3) les essais cliniques qui changeraient la pratique de la prise en charge des patients souffrant d'insuffisance cardiaque. Premièrement, tous les patients souffrant d'insuffisance cardiaque et d'anémie devraient être examinés en vue d'éliminer les causes réversibles de l'anémie. Deuxièmement, les patients souffrant d'insuffisance cardiaque chronique stable devraient subir une analyse du peptide natriurétique. Troisièmement, l'attention devrait être portée au traitement des patients sélectionnés souffrant d'insuffisance cardiaque et d'une fonction systolique préservée par un antagoniste du récepteur minéralocorticoïde, et au traitement des patients souffrant d'insuffisance cardiaque et d'une fraction d'éjection réduite par un inhibiteur des récepteurs de l'angiotensine/inhibiteur de la néprilysine lorsque le médicament est approuvé. Comme les mises à jour des années précédentes, les sujets ont été choisis en réponse à la rétroaction des parties prenantes. La mise à jour de 2014 comprend les recommandations, les valeurs et les préférences, ainsi que les conseils pratiques pour aider les cliniciens et les professionnels de la santé à mieux prendre en charge les patients souffrant d'insuffisance cardiaque.

Since 2006, the Canadian Cardiovascular Society (CCS) has published heart failure (HF) management guidelines as part of a commitment to a multiyear, closed-loop initiative to provide support for the best practice of HF management.[1] The CCS has also implemented the National Heart Failure Workshop Initiative; a series of case-based workshops to discuss how to implement guidelines and identify challenges facing health care providers. Feedback from these

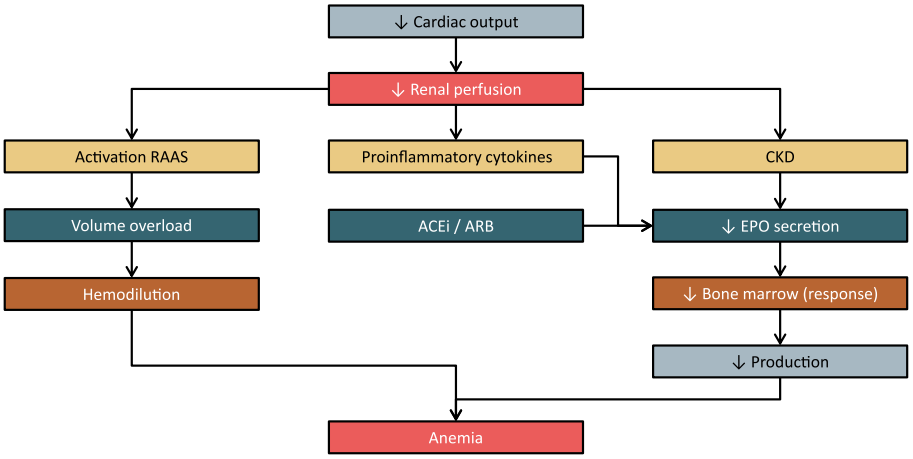

Figure 1. Mechanism of the development of anemia in heart failure. ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CKD, chronic kidney disease; EPO, erythropoietin; RAAS, renin angiotensin aldosterone system.

sessions, together with specific solicited input from key stake holders, formed the templates for topics covered annually in subsequent years. These annual updates have produced a series of evidence-based articles with recommendations and practical tips outlining suggestions for HF management.[2-8]

The constitution of the primary and secondary panels, systematic review strategy, and methods for formulating the recommendations, values, and preferences and practical tips are described in detail on the CCS website (www.ccs.ca).

Since 2011, the HF management recommendations have been made using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[9] The GRADE system classifies the quality of evidence as high (further research very unlikely to change confidence in the estimate of effect), moderate (further research likely to have an important effect on confidence in the estimate of effect and might change the estimate), low (further research very likely to have an important effect on confidence in the estimate of effect and likely to change the estimate), and very low (estimate of the effect very uncertain). The GRADE system offers 2 grades of recommendations: "strong" (desirable effects clearly outweigh undesirable effects or clearly do not) and "weak" or "conditional," when trade-offs are less certain, either because of low-quality evidence or because the evidence suggests desirable and undesirable effects are closely balanced, and weak recommendations become mandatory. Furthermore, since 2012 the Committee has included values and preferences, which complement the GRADE system of recommendations. Recommendations are not given in areas in which the evidence is believed to be inadequate.

The objectives of the 2014 CCS HF consensus update were to provide a review of HF management and recommendations in 3 areas: (1) management of anemia; (2) the optimal use of biomarkers, particularly natriuretic peptides (NPs); and (3) recently published clinical trials that might change practice.

Anemia in HF

HF is a complex syndrome with effects beyond the myocardium and vasculature. Although treatments that improve survival, exercise capacity, and reduce hospitalizations have been established, the increased complexity of patients with their comorbidities often confounds treatment. These comorbidities become risk factors for future deterioration and might contribute to clinical deterioration, complicate management, or are associated with poorer prognosis. Anemia has been linked to a decrease in survival and an increase in hospitalizations.[10]

Epidemiology and mechanisms

Anemia is often defined according to knowledge of normal, age- and sex-specific values of hemoglobin, or hematocrit. The World Health Organization defines anemia as a hemoglobin value $<$ 130 g/dL for men and 120 g/dL for women; other definitions also exist.[11]

The prevalence of anemia in patients with HF varies between 10% and 49%.[12,13] One meta-analysis including 153,180 patients has reported a prevalence of 34%[14] and data from patients with new-onset HF reported a prevalence of 17%.[10] The reason for the variability in these reports are based on the definitions used, the ratio of women to men, and the percentage of elderly patients or patients with renal disease in the cohort (anemia is more prevalent in all of these subgroups).[15] Another important factor is the difference between early and advanced HF, which can influence hemoglobin concentration (often called pseudoanemia or hemodilution).[16] Additionally, hemoglobin and hematocrit are dynamic markers and might respond to differences in the status of the underlying aetiology of anemia. A study of patients with HF, free of anemia at the time of diagnosis, demonstrated that up to 20% would become anemic in 6 months.[17]

There appears to be a similar prevalence of anemia in patients with HF with preserved ejection fraction (HF; HFpEF) and reduced EF (HFrEF). For example, mean hemoglobin levels have been reported to be 125 g/dL for

patients with HFrEF and 118 g/dL in patients with HFpEF.[18] The effect of anemia on prognosis is similar for HFpEF and HFrEF—patients with anemia fare worse in terms of mortality, hospitalization, or functional capacity than those who are not anemic, regardless of systolic function.[19]

As shown in Figure 1, there are multiple mechanisms in HF that could result in anemia. The reduction of cardiac output might result in a decrease of renal blood flow and further activation of the renin angiotensin aldosterone system. Normally, this reduction in flow will result in an increase in erythropoietin (EPO) levels. In HF, this increase is, however, not necessarily associated with an increase in hemoglobin because of a decreased sensitivity of bone marrow to EPO.[20] In patients hospitalized with acute HF, New York Heart Association (NYHA) functional class is correlated with the level of EPO, increased levels of natriuretic peptides (NPs), and inversely related to hemoglobin levels.[21] A recent study has demonstrated that anemia is strongly associated with markers of more advanced heart disease, and not only with the level of renal dysfunction in patients with HFrEF. Increased myocardial remodelling, inflammation, and volume overload are the hallmarks of patients with anemia and HF.[22]

Treatment of anemia in HF

RECOMMENDATIONS

1. We suggest that for patients with documented iron deficiency, oral or intravenous iron supplement be initiated to improve functional capacity. (Weak Recommendation; Low-Quality Evidence).
2. We recommend erythropoiesis stimulating agents not be routinely used to treat anemia in HF. (Strong Recommendation; High-Quality Evidence).

Values and Preferences. The iron supplement recommendation was derived mostly from the experience of clinicians, small clinical trials, and 2 large randomized controlled trials (RCTs). The recommendations against the use of erythropoiesis-stimulating agents (ESAs) were derived from robust data from RCTs.

Practical Tip: Patients with severe chronic kidney disease and anemia should be referred to a nephrologist to seek the optimal therapy for anemia.

Symptomatic patients with low transferrin and/or ferritin levels should be considered for supplementary iron therapy principally with a goal of improving symptoms.

Suggested investigations of anemia are summarized in Supplemental Table S1. After excluding obvious causes of anemia, the clinician is left with the decision of whether to treat the anemia. Current treatment options include evaluation of the contribution of volume overload, concomitant medications (especially antiplatelet agents and anticoagulants), oral or intravenous iron supplements, and re-evaluation of optimal HF therapy.

Concomitant medications

Patients with HF and anemia should have a full review the indications of all medications, including the absolute need for antiplatelet and anticoagulant agents and other drugs that might cause anemia such as ribavirin and phenytoin. Although angiotensin-converting enzyme (ACE) inhibitors have been associated with anemia,[23] the relative effect on hemoglobin levels appears to be mild and does not necessarily make this class of drugs less effective in HF therapy nor should it alter therapy.

Oral and intravenous iron supplementation

Oral iron supplementation has not been extensively studied in patients with HF to evaluate the effects on clinically important outcomes. Although correction of anemia is linked to improved left ventricular remodelling,[24] variability in the results reported with the use of iron in patients with HF might be related to the agent used (iron sulphate, fumarate, succinate, or gluconate) or the route of administration,[25] which influence the variability in absorption and tolerability. Evidence suggests that improvement in quality of life and exercise tolerance might be achievable with use of oral iron supplementation.[25]

All intravenous iron agents are colloids that consist of iron-carbohydrate nanoparticles. They are iron dextran, gluconate, sucrose, or ferric carboxymaltose. Serious side effects, particularly anaphylactic reactions, have been reported with use of iron dextran, the use of which has been largely abandoned. More recently, the results of a study on correction of iron deficiency with ferric carboxymaltose have been published. The **F**erinject **A**ssessment in Patients with **I**ron Deficiency and Ch**R**onic **H**eart **F**ailure (FAIR-HF) was a multicentre, double-blind, placebo-controlled trail of 459 patients with NYHA class II-III symptoms with and without anemia, with a serum ferritin level < 100 ug/L (or transferrin saturation $< 20\%$ if serum ferritin between 100 and 299 ug/L) were randomized to intravenous iron vs placebo (2:1 ratio) for 24 weeks.[26] This trial demonstrated an improvement in indicators of quality of life and 6-minute walk distance, but was not powered to detect a difference in hospitalizations or death. There was, however, no significant difference in mortality, or cardiovascular-related hospitalizations over 6 months. The Ferric **C**arboxymalt**O**se evaluatio**N** on per**F**ormance in patients with **IR**on deficiency in co**M**bination with chronic **H**eart **F**ailure (CONFIRM-HF) was a multicentre, double-blind, placebo-controlled trial conducted on 304 ambulatory symptomatic HF patients with left ventricular EF (LVEF) $\geq 45\%$, increased natriuretic peptide (NP) levels, and iron deficiency (ferritin, 100 ng/mL or 100-300 ng/mL if transferrin saturation $< 20\%$).[27] Patients were randomized to treatment with intravenous iron, as ferric carboxymaltose or placebo for 52 weeks. The primary end point was the change in 6-minute walk test distance from baseline to 24 weeks, and secondary end points were assessed at 24 and 52 weeks. Treatment with intravenous iron significantly prolonged 6-minute walk test distance at 24 weeks (the difference between intravenous iron vs placebo was 33 ± 11 m; $P = 0.002$). The treatment effect of intravenous iron was consistent in all subgroups and was sustained to 52 weeks

(the difference between intravenous iron vs placebo was 36 ± 11 m; $P < 0.001$). Improvement in NYHA class, Patient Global Assessment, quality of life, and Fatigue Score in patients treated with intravenous iron was observed with statistical significance observed from week 24 onward. Treatment with intravenous iron was associated with a significant reduction in hospitalization for worsening HF. The number of deaths and the incidence of adverse events were similar. There are other small studies that have demonstrated improvement in quality of life with intravenous iron as summarized in a systematic review and meta-analysis.[28]

ESAs

ESAs have been studied as a potentially promising class of agent to improve hemoglobin in different disease states. The 2 largest trials on the role of ESAs in HF are the Study of Anemia in Heart Failure Trial (STAMINA-HeFT)[29] and **R**eduction of **E**vents With **D**arbepoetin Alfa in **H**eart **F**ailure (RED-HF) trial.[30] These 2 trials, and a meta-analysis[31] failed to demonstrate benefits in mortality, cardiovascular events, and hospitalizations. In RED-HF, a significant increase in thromboembolic events was found in patients with hemoglobin levels > 130 g/dL.[30] Based on the results of those studies, it is unlikely that another morbidity or mortality study will be undertaken with results that will support the use of ESAs in HF.

Optimal Use of Biomarkers in HF

Establishing diagnosis and selecting optimal therapy for any patient are current challenges, because the costs associated with HF diagnostic and therapeutic strategies continue to increase. Biomarkers might help stratify risk and individualize therapy.[32] In this update, the role of circulating biomarkers for the management of patients with HF are reviewed, with a focus on their role in monitoring for disease progression.

NPs

RECOMMENDATIONS

1. We recommend that B-type NP (BNP)/amino-terminal fragment of propeptide BNP (NT-proBNP) levels be measured to help confirm or rule out a diagnosis of HF in the acute or ambulatory care setting in patients in whom the clinical diagnosis is in doubt (Strong Recommendation; High-Quality Evidence).
2. We recommend that measurement of BNP/NT-proBNP levels be considered in patients with an established diagnosis of HF for prognostic stratification (Strong Recommendation; High-Quality Evidence).

Values and Preferences. These recommendations remain unchanged from previous CCS HF guidelines. The levels of NPs for ruling in and ruling out a diagnosis of HF are shown in Table 1.

Table 1. Natriuretic peptides cut points for the diagnosis of heart failure

	Age, Years	HF is unlikely	HF is possible but other diagnoses need to be considered	HF is very likely
BNP	All	< 100 pg/mL	100-500 pg/mL	> 500 pg/mL
NT-proBNP	< 50	< 300 pg/mL	300-450 pg/mL	> 450 pg/mL
	50-75	< 300 pg/mL	450-900 pg/mL	> 900 pg/mL
	> 75	< 300 pg/mL	900 - 1800 pg/mL	> 1800 pg/mL

BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, amino-terminal fragment propeptide B-type natriuretic peptide.

Increased myocardial wall stress due to volume or pressure overload activates the BNP gene in cardiac myocytes, producing the intracellular precursor propeptide (proBNP). Cleavage releases the biologically active BNP and biologically inert NT-proBNP.[33] BNP stimulates natriuresis and vasodilation with consequent afterload reduction, inhibits renin-angiotensin-aldosterone release and sympathetic nervous activity, and reduces fibrosis.[33]

BNP and NT-proBNP levels are increased in HFrEF and HFpEF, although the levels are lower on average in individuals with HFpEF.[34,35] Additionally, a number of demographic and clinical variables have been described that might result in higher or lower levels of circulating NP levels in patients with HF.[36-42]

Previous recommendations from the CCS have highlighted the utility of NPs in patients in whom the diagnosis of HF might remain unclear, and the prognostic significance of increased levels of NPs.[2,7] The recommendations remain unchanged from previous ones with the exception that they are now presented in the GRADE format. The levels for diagnosis of HF are shown in Table 1.

BNP and NT-proBNP are among the most powerful independent predictors of mortality, adverse cardiovascular events, and health care resource utilization across the spectrum of HF severity, providing incremental prognostic information beyond traditional covariables and risk stratification models.[43-46] Furthermore, RCTs in patients with acute dyspnea have demonstrated that NP testing when used with conventional management is superior to conventional management alone in improving clinical outcomes and reducing cost.[47,48] However, the role of biomarkers including NP in the management of patients with acute cardiovascular symptoms in the ambulance before arrival at the hospital is still unclear.[49] Importantly, the optimal strategy to fully incorporate these research data into everyday clinical practice in terms of guiding therapy in patients with stable chronic HF remains uncertain.

NP-guided management

RECOMMENDATIONS

1. We suggest, in ambulatory patients with HF due to systolic dysfunction, measurement of BNP or NT-proBNP to guide management should be considered to decrease HF-related hospitalizations and potentially reduce mortality. The benefit is uncertain in

individuals older than 75 years of age (Weak Recommendation; Moderate-Quality Evidence).

Values and Preferences. These recommendations are based on multiple small RCTs, most of which demonstrated benefit, and 3 meta-analyses, which universally demonstrated benefit. It is realized that there is still a large RCT ongoing that might modify the conclusions.

In HF, disease management programs have been shown to improve patient care and adherence to guidelines.[50] Optimal dosing of recommended therapy relies on evidence derived from RCTs. A management strategy guided by using circulating levels of NPs has been proposed to reduce the risk of adverse clinical events. Multiple RCTs of NP-guided management have been published, using different trial designs, NP assays, and target NP levels.[51-59]

In the **T**rial of **I**ntensified vs Standard **ME**dical Therapy in Elderly Patients With **C**ongestive **H**eart **F**ailure (TIME-CHF),[57] ambulatory patients with chronic HF due to systolic dysfunction were enrolled; the study showed that NT-proBNP-guided vs symptom-guided HF management did not improve overall clinical outcomes (survival free of all-cause hospitalizations and quality of life) over 18 months. However, there were fewer HF hospitalizations in patients in the NT-proBNP-guided group.[57] These benefits were possibly attributable to more intensified HF medical therapy in the NT-proBNP-guided group and did not disappear after cessation of the NT-proBNP-guided strategy.[60] Interestingly, the use of NT-proBNP-guided HF therapy improved outcomes in patients aged 60-75 years but not in those 75 years old and older ($P = 0.02$ for interaction).[57]

The NT-pro**B**NP-**A**ssisted **T**reatment **T**o **LE**ssen **S**erial **CAR**diac **RE**admissions and **D**eath (BATTLESCARRED) trial was a RCT that compared usual care, intensive standardized clinical management, and NT-proBNP-guided therapy for HF.[55] NT-proBNP-guided management was accompanied by a lower mortality at 3 years compared with either intensive clinical management or usual care in patients aged $\leq$ 75 years. The positive effects of NT-proBNP-guided management were maintained after cessation of the guided strategy.

A more aggressive uptitration of HF medical therapy appears to be one of the factors responsible for the positive effects of NP-guided management, leading to higher target doses of guideline-recommended HF therapy achieved. Patient age has a modulating effect on the clinical efficacy of NT-proBNP-guided therapy. In the 2 previously discussed trials,[55,57] benefits were confined to patients $\leq$ 75 years of age, and previous positive studies also enrolled younger patients (average age, 66-70 years). One explanation for this observation is that older patients are less likely to tolerate target doses of evidence-based agents. Reduced renal function can also contribute to more frequent adverse effects and to therapeutic nihilism in older patients. In addition, HFpEF is more prevalent among the elderly and evidence-based therapy is sparse for this type of HF. These findings suggest that stringent intensification of HF medication might be best guided using additional information in elderly patients.

Marked NT-proBNP reductions (> 50%, from a median baseline of 2344 pg/mL) were achieved in the **PR**oBNP **O**utpatient **T**ailor**E**d Chronic Heart Failure **T**herapy (PROTECT) study[53] with associated reductions in cardiovascular events. However, 56% of patients in the NP-guided arm did not reach the target NT-proBNP (< 1000 pg/mL). More patients attained the desired NP levels in the studies when more liberal or even individualized NP targets were applied, but this was not associated with reduced clinical events. In the Can **PR**o-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure **I**mprove Heart Failure Morbidity and **M**ort**A**lity (PRIMA) study,[52] the lowest NT-proBNP level within 2 weeks after hospital discharge was used as the baseline (median, 2491 pg/mL), and uptitration was recommended if the outpatient level was > 850 pg/mL. No difference was noted in the primary end point (days alive and out of hospital) between a NP-guided strategy and the control arm, despite greater uptitration of inhibitors of the renin-angiotensin system (RAS) and in diuretic doses in the NT-proBNP group. The other trials that used individualized targets, the **S**trategies for **T**ailoring **A**dvanced Heart Failure **R**egimens in the Outpatient Setting: **BRa**In Na**T**riur**E**tic Peptide versus Clinical Congestion Score (STARBRITE) trial[58] and the **S**wedish **I**ntervention study—**G**uidelines and **N**T-proBNP **A**na**L**ysis in **H**eart **F**ailure (SIGNAL-HF) trial,[56] led to similar results. Figure 2 summarize the results of NP-guided therapy trials in the most recent meta-analysis.[61]

Results of the trials mentioned herein and 3 systematic reviews and meta-analyses that synthesized the RCT results, benefits of NP-guided therapy have been shown to improve survival and reduce hospitalization (Fig. 2).[61-63] In these studies, NP-guided therapy had no benefit in 2 subgroups: age > 75 years and those with HFpEF. Consequently, a larger multicentre trial of a single-target NP level (NT-proBNP 1000 pg/mL) and the use of guideline-approved therapies in both treatment arms is now under way and includes Canadian sites, the **GUID**ing Evidence Based Th**E**rapy Using Biomarker **I**ntensified **T**reatment (GUIDE-IT; www.clinicaltrials.gov, NCT01685840). The single-centre **EX**tended **IMPROVE**ment in Clinical Outcomes of Patients with **C**hronic **H**eart **F**ailure using Serial NT-proBNP Monitoring (EX-IMPROVE-CHF; www.clinicaltrials.gov, NCT00601679) will also help clarify the role of NP-guided therapy in HF management.

Hospital predischarge NP measurements

RECOMMENDATIONS

1. We suggest that measurement of BNP or NT-proBNP in patients hospitalized for HF should be considered before discharge, because of the prognostic value of these biomarkers in predicting rehospitalization and mortality (Strong Recommendation; Moderate-Quality Evidence).

Values and Preferences. This recommendation is based on multiple small RCTs, all of which demonstrated an association with clinical outcomes. Although the risk of readmission is decreased with lower NP levels, clinicians should also consider the limitations of delaying discharge from the hospital for this purpose.

Practical Tip: We suggest that individuals with risk factors for the development of HF, NP levels be used to implement strategies to prevent HF. An increased level of NP of BNP > 100 pg/mL and NT-proBNP > 300 pg/mL, higher values than those used in the 2 trials discussed below to avoid over screening, along with the presence of risk factors for HF, should at least trigger more intensive follow-up (see Prevention of HF).

A change of 30% in NP level likely exceeds the day-to-day variation and is in general considered relevant.[64] For ambulatory patients with HF who are evaluated in the clinic, a NP level that increases more than 30% should therefore call for more intensive follow-up and/or intensified medical treatments, even if they are not congested clinically. The latter can include diuretic therapy or intensification of ACE inhibitors, β-blockers, and mineralocorticoid receptor antagonists if their doses are not yet at the targets defined in clinical trials.

For patients who are about to be discharged from the hospital, physicians should ensure that the patients are relatively free from congestion clinically and with a NP level that is significantly lower than that on admission for HF. A suggested algorithm for management of different stages of HF using NP is shown in Figure 3.

Besides predicting prognosis of patients in general, BNP level obtained before discharge has been associated with mortality and rehospitalization.[43,65] Indeed, predischarge NP in conjunction with change in NP has now been incorporated into a risk score for death and readmission of HF in patients admitted with HF.[66]

Prevention of HF

Two trials have tested the approach of using NPs as part of a strategy to prevent the development of HF. The role of BNP in prevention of HF was recently evaluated in the Saint Vincent **S**creening **to** **P**revent **H**eart **F**ailure (STOP-HF) trial[67] in which asymptomatic individuals at high risk for the development of HF (such as hypertension, hypercholesterolemia, obesity, known vascular disease, diabetes, arrhythmia requiring treatment, or valvular abnormalities) were randomly assigned to receive usual care vs BNP testing. In the intervention arm, individuals with increased levels of BNP (> 50 pg/mL) received echocardiography and additional health care services based on a shared care approach, including introduction of RAS antagonists. The primary end point of left ventricular dysfunction with or without HF was met in 59 (8.7%) of 677 individuals in the control group and 37 (5.3%) of 697 in the intervention group (odds ratio, 0.55; 95% confidence interval [CI], 0.37-0.82; $P = 0.003$). The incidence rate of emergency hospitalization for major cardiovascular events was 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; 95% CI, 0.45-0.81; $P = 0.002$).

In the NT-**Pr**O**B**NP Guided Primary Preve**NT**ion of CV Events **I**n Di**A**beti**C** Patients (PONTIAC) trial,[68] 300 patients with type 2 diabetes, increased level of NT-proBNP (> 125 pg/mL) but free from cardiac disease were randomized to either standard treatment at diabetes care units or an "intensified" strategy in which patients were additionally treated at a cardiac outpatient clinic for the uptitration of RAS inhibitors and β-blockers. The primary end point of hospitalization/death due to cardiac disease at 2 years was significantly reduced with use of the intensified strategy (hazard ratio [HR], 0.35; 95% CI, 0.13-0.98; $P = 0.044$). End points of all-cause hospitalization and unplanned cardiovascular hospitalizations or death were also reduced ($P < 0.05$ for all). There were no significant changes in NT-proBNP levels in both groups, and no differences between groups in that respect. The preliminary results of STOP-HF and PONTIAC suggest that a NP-guided strategy for at-risk individuals might provide benefit in preventing and treating HF, leading to reductions in cardiac mortality and hospitalizations.

Other Biomarkers

As highlighted in previous guidelines,[6] renal function has important prognostic implications in HF, as shown in a systematic review and meta-analysis.[69] Although the more recently studied renal function-related markers such as neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C could provide earlier (NGAL) or more sensitive (cystatin C) detection of changes in renal function, and these biomarkers have, however, been shown to improve risk stratification in multiple studies, especially for mortality,[70,71] there is no evidence that using these markers in clinical practice would improve outcomes (Table 2).

High-sensitivity assays to measure circulating cardiac troponins have gained popularity. Cardiac troponins are increasingly detectable in patients with HFrEF in proportion to HF severity. In the **Val**sartan in **He**art **F**ailure **T**rial (ValHeFT), 10.4% of subjects had detectable troponin T with a fourth-generation clinical assay; however, this proportion increased to 92% when a high-sensitivity assay was used.[72] The degree of high sensitivity cardiac troponin (hs-cTn) increase appears to be a powerful predictor of mortality and cardiovascular events in ambulatory and acutely decompensated patients with chronic HFrEF, even after adjustment for traditional risk predictors including NPs.[73-75] Distinguishing the increase in acute HF from that in myocardial infarction could be challenging; chest pain and concomitant electrocardiographic changes would favour myocardial infarction. There currently is not enough evidence to support serial measurement of troponins for risk stratification of patients with chronic HF in clinical practice (Table 2), because changes in high sensitivity cardiac troponin T (hs-cTnT) concentration only modestly improve prognostic discrimination beyond other known prognostic markers (mainly for fatal outcomes).

Soluble toll-like receptor-2 (ST2) is a transmembrane receptor belonging to the interleukin-1 receptor family that regulates inflammation and immunity.[76,77] Soluble ST2 promotes cardiac hypertrophy, fibrosis, and ventricular dysfunction.[78] Expression of ST2 is induced by mechanical myocyte stress and circulating levels are increased in relation to measured diastolic load.[79] In HFrEF, serum levels of soluble ST2 are independently associated with mortality and disease progression and provide incremental prognostic value over NT-proBNP.[80] A potential useful property of ST2 is that

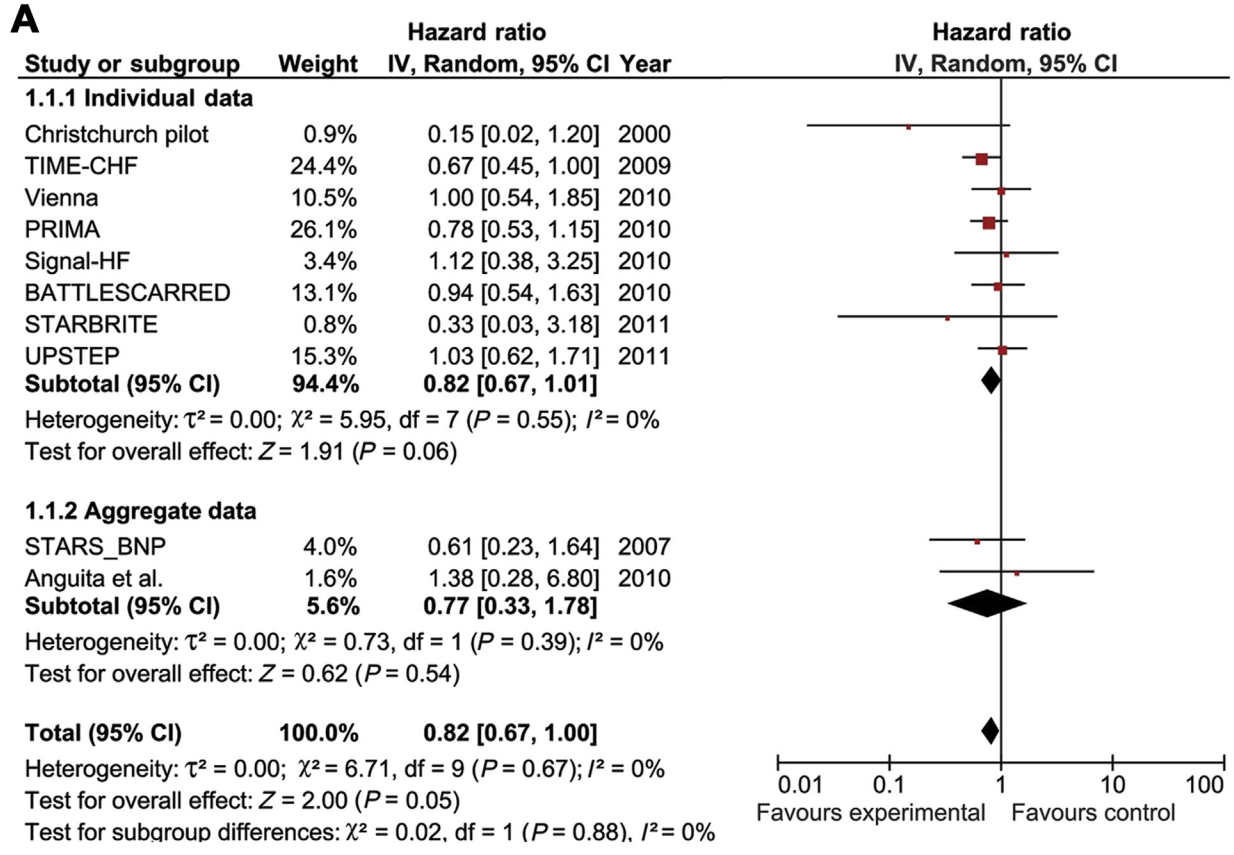

Figure 2. Forest plot of (**A**) the primary end point, all-cause mortality; and (**B**) the secondary end point, heart failure hospitalization. Reproduced with permission from Troughton et al.[61]

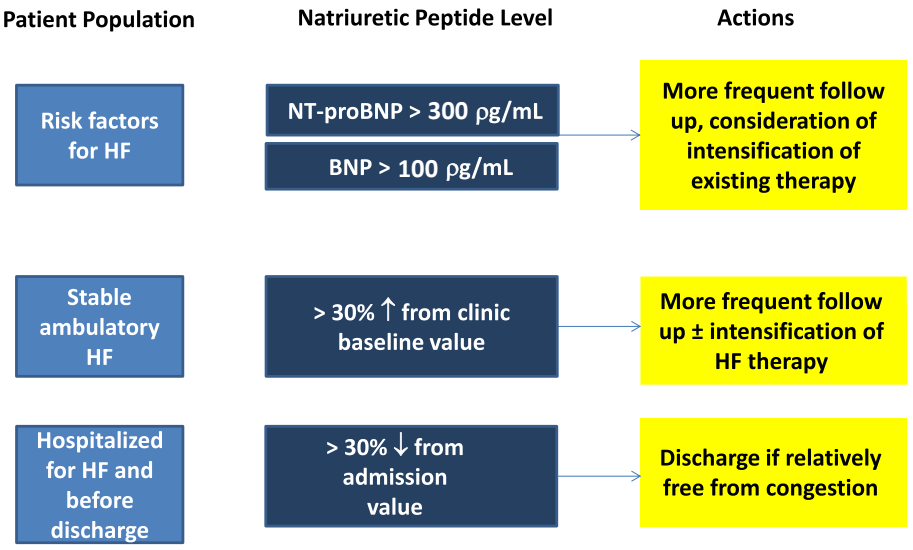

Figure 3. Algorithm of the use of natriuretic peptide in the prevention and management of ambulatory and hospitalized patients with heart failure. Clinical evaluation and the risks and benefits of the action suggested should be considered. BNP, B-type natriuretic peptide; HF, heart failure; NT-proBNP, amino-terminal fragment propeptide B-type natriuretic peptide.

it has a relatively low week-to-week variation in circulating levels[81] and therefore the potential to improve long-term prognostication of ambulatory HF patients with renal insufficiency.[82] In a prospective cohort of 1821 chronic HF patients recruited from tertiary clinics, Basuray and colleagues recently have shown that ST2 levels were higher in HFpEF than in HFrEF patients, and intermediary levels were observed in patients with previously low EF (or "HF-recovered EF"). The risk of cardiac hospitalization was similar in patients with HF-recovered EF than in those with HFpEF.[83] Therefore, ST2 could be a marker of residual risk in patients with previously low EF.

Galectin-3 (Gal-3) is a fibrosis biomarker related to prognosis in chronic HF but a head-to-head comparison of ST2 and Gal-3 in 876 patients with chronic systolic HF[84] recently revealed superiority of ST2 over Gal-3 in risk stratification. Gal-3 provided trivial incremental predictive contribution to existing clinical risk factors. In this study,

Table 2. Selected biomarkers with potential for future clinical use in the management of heart failure

Biomarkers	Pathophysiological pathways/comorbid conditions with prognostic implications	HF populations targeted	Advantages	Potential benefits	Challenges before implementation
NGAL	Renal function	Acute HF	Early detection of renal function deterioration	Adjusting therapy to improve prognosis by avoiding acute renal failure progression	Unclear if using NGAL in acute HF to modify therapies improves clinical outcomes
Cystatin C	Renal function	Acute and chronic HF	More sensitive detection of changes in renal function	Same as above	Unclear if using cystatin C, over using eGFR, to modify clinical management provides further clinical benefit
Cardiac hs-troponins	Myocyte death	Acute and chronic HF	Very sensitive marker predicting higher risk of CV events regardless of aetiology	Optimization of therapy in patients with elevated hs-cTn should be more aggressive	Prognostication improves only for mortality and use to modify therapy has not been tested
ST2	Fibrosis/inflammation/ immunity	Acute and chronic HFrEF, HFpEF, and previously low EF recovered	Additional prognostic value beyond NPs suspected low week-to-week variations	Could provide additional value for short and long term prognostication, regardless of LVEF	Unclear if using ST2 in acute HF to modify therapies improves clinical outcomes
Galectin-3	Cardiac and vascular fibrosis	Incident HF, HFrEF and HFpEF	Early detection of risk and long term prognostication in HF	Preventive measures and therapy optimization based on levels could improve outcomes	Recent study showed ST2 superior to galectin-3 in a multivariable prediction model

CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs, high-sensitivity; hs-cTn, high sensitivity cardiac troponin; LVEF, left ventricular ejection fraction; NGAL, neutrophil gelatinase-associated lipocalin; ST2, soluble toll-like receptor-2.

ST2 was incorporated in a model that included NT-proBNP. Whether the addition of ST2 to clinical management would modify outcomes at all stages of HF and improve candidate selection for specific therapies remains to be demonstrated (Table 2).

There is a need to improve optimization of therapy and prognosis in HF. Although a myriad of circulating biomarkers are becoming increasingly attractive, integrating their use in clinical practice remains difficult. The incremental prognostic value of novel biomarkers above and beyond what is obtained from established risk predictors must be clearly demonstrated, and the clinical effect of use of such biomarkers must then be tested in a wide spectrum of HF patients before they can eventually be incorporated in clinical decision-making.[32] These steps have been accomplished, in many regards, for the NPs. Hence, it is now time to implement their use in HF, at least in settings in which the evidence is most robust, such as in emergency departments and in patients hospitalized with HF.

Despite the evidence, NP testing is not widely available in Canada. A NP-guided strategy for the diagnosis of HF is cost effective in the Canadian environment.[47] National registries to assess the outcomes of a broader population of patients with HF after hospitalization, and the overall costs incurred by health systems, patients, and providers could further inform the best practice profile for the use of NPs.

Clinical Trials That Might Influence Practice

Mineralocorticoid receptor antagonists in HFpEF

Patients with HFpEF have no therapies proven to reduce the morbidity or mortality associated with this disease. Mineralocorticoid receptor antagonists have been proposed, and several trials have been completed.[85,86] The largest of these trials is TOPCAT, a randomized, double-blind, placebo-controlled trial of spironolactone in 3445 patients with HFpEF (key inclusion criteria, age $\geq$ 50 years; NYHA functional class II-IV; serum potassium $<$ 5.0 mmol/L; eGFR $\geq$ 30 mL/min, or serum creatinine $<$ 221 μmol/L; LVEF $\geq$ 45%; and hospitalization for HF in the previous year or increased NP level [BNP $\geq$ 100 pg/mL, NT-proBNP $\geq$ 360 pg/mL]). Although there are currently no medications directly indicated for HFpEF, $>$ 80% were already receiving ACE inhibitor/angiotensin receptor blockers and $>$ 70% were receiving β-blockers for other indications. Patients were randomized to placebo or spironolactone (15-45 mg daily; target dose, 30 mg; mean dose achieved, 25 mg/d) and had a mean follow-up of 3.3 years. The primary end point (composite of death from cardiovascular causes, aborted cardiac arrest, hospitalization for HF) occurred in a total of 671 patients, with an 11% reduction favouring spironolactone (HR, 0.89; 95% CI, 0.77-1.04) that was not significant (P = 0.14). Of the key components of the primary end point, none were significantly different except for HF hospitalizations (HR, 0.83; 95% CI, 0.69-0.99; P = 0.04).

Two other observations are important to the interpretation of the TOPCAT trial. First, 28.5% of patients entered the clinical trial based on increased levels of BNP/NT-proBNP, and these patients had a significant 35% reduction in the primary end point (HR, 0.65; 95% CI, 0.49-0.87; P = 0.003). Patients enrolled via a previous hospitalization for HF did not have a reduction in the primary end point (HR, 1.01; 95% CI, 0.84-1.21; P = 0.923).

Second, there were marked geographic differences in the baseline characteristics, enrollment stratum of BNP/NT-proBNP, or previous hospitalization, and therefore, potential event rates between patients enrolled in the Americas and those enrolled in Russia or Georgia. These differences have led to the inclusion of region as a variable in a post hoc adjustment model, resulting in a 15% relative risk reduction for the primary end point in favour of spironolactone (HR, 0.85; 95% CI, 0.73-0.99; P = 0.043).

Similar to other trials of mineralocorticoid receptor antagonists, there was a doubling in the rate of hyperkalemia (9.1% in the placebo group and 18.7% in the spironolactone group), fewer events of hypokalemia, no significant incidence of renal failure leading to dialysis, and no deaths due to hyperkalemia.

RECOMMENDATIONS

1. We suggest that in individuals with HFpEF, an increased NP level, serum potassium $<$ 5.0 mmol/L, and an estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min, a mineralocorticoid receptor antagonist like spironolactone should be considered, with close surveillance of serum potassium and creatinine (Weak Recommendation; Low-Quality Evidence).

Values and Preferences. This recommendation is based on a prespecified subgroup analysis of the **T**reatment **O**f **P**reserved **CA**rdiac Function Heart Failure with an Aldos**T**erone Antagonist (TOPCAT) trial, which includes analysis of the predefined outcomes according to admission NT-proBNP level, and the corroborating portion of the trial conducted within North and South America.

Practical Tip: After spironolactone is started and with a change in dose, serum potassium and creatinine should be monitored in the first week, fourth week, and then fourth month, and whenever clinically indicated. In practice, spironolactone is available in 25-mg tablets. The dose to use will therefore be 25-50 mg per day.

Combined angiotensin/neprilysin inhibition in HFrEF

RECOMMENDATIONS

1. We recommend that in patients with mild to moderate HF, an EF $\leq$ 40%, an elevated NP level or hospitalization for HF in the past 12 months, a serum potassium $<$ 5.2 mmol/L, and an eGFR $\geq$ 30 mL/min and treated with appropriate doses of guideline-directed medical therapy should be treated with LCZ696 in place of an ACE inhibitor or an angiotensin receptor blocker, with close surveillance of serum potassium and creatinine (Conditional Recommendation; High-Quality Evidence).

Values and Preferences. This recommendation places high value on medications proven in large trials to reduce mortality, HF rehospitalization, and symptoms. It also considers the health economic implications of new medications. The recommendation is conditional because the drug is not yet approved for clinical use in Canada and the price is still not known.

ACE inhibitors are the cornerstone of therapy in HF. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including NPs, bradykinin, and adrenomedullin.[87] Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling.[88] Combined inhibition of the renin-angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies,[89] but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema.[90,91]

The **P**rospective Comparison of **ARNI** (Angiotensin Receptor-Neprilysin Inhibitor) with **A**CEI (Angiotensin-Converting—Enzyme Inhibitor) to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure Trial (PARADIGM-HF) compared the angiotensin receptor blocker neprilysin inhibitor LCZ696 with enalapril in patients who had HF with a reduced LVEF.[92] In this trial, 8442 patients with HF, NYHA class II, III, or IV, and LVEF $\leq$ 40% were randomized double-blind to either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily) in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF.

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months. The primary outcome occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (HR, 0.80; 95% CI, 0.73-0.87; $P < 0.001$). A total of 711 patients (17.0%) who received LCZ696 and 835 patients (19.8%) who received enalapril died (all-cause death: HR, 0.84; 95% CI, 0.76-0.93; $P < 0.001$); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (HR, 0.80; 95% CI, 0.71-0.89; $P < 0.001$). Compared with enalapril, LCZ696 also reduced the risk of hospitalization for HF by 21% ($P < 0.001$) and decreased the symptoms of HF ($P = 0.001$). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but a smaller risk of renal impairment, hyperkalemia, and cough than the enalapril group.

Clinical implications

Patients in this trial and the absolute benefit were quite comparable with those in other trials that changed clinical practice, including trials of ACE inhibitors, β-blockers, and mineralocorticoid anatagonists.[92] Because of the size of the trial, the use of a gold-standard active control of high-dose enalapril and the magnitude of benefit for mortality end points, the trial will modify clinical practice. The dual action of this drug might translate into greater long-term survival of patients. Although it would be preferable to see validation in another trial, the totality of data would suggest that the drug should be recommended for use in HF when it is approved.

Conclusions

The 2014 HF guideline update provides the following recommendations. All patients with HF and anemia should be investigated for reversible causes of anemia. Patients with chronic stable HF should undergo NP testing to monitor progress and hospitalized patients should have testing before discharge. Finally, considerations should be given to treat selected patients with HF and preserved systolic function with a mineralocorticoid receptor antagonist, and to treat patients with HF and reduced systolic function with a combined angiotensin/neprilysin inhibitor, when the drug is available.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.10.022.