Optimizing health outcomes in heart failure and multimorbidity: A multidisciplinary expert, consensus, scientific statement (Abridged Version)

A. Authors

The authors comprise a multidisciplinary team of health care professionals (including Cardiologists, Geriatricians, Internal Medicine Specialists, Nurses and Human Movement Specialists) with an active interest and expertise relevant to multimorbidity and heart failure (HF) - Simon Stewart, Barbara Riegel, Cynthia Boyd, Yasmin Ahamed, David R Thompson, Louise Burrell, Melinda J Carrington, Andrew JS Coats, Bradi Granger, Julie Hides, William Weintraub, Debra K Moser, Victoria Vaughan & Michael Rich.

B. Brief Background

As described in the main application documents, multimorbidity in HF, defined by the *presence of HF of any etiology and two or more concurrent conditions that require active management*, represents a growing problem within the ageing HF patient population. Expert guidelines struggle to articulate how this multi-factorial problem can be effectively addressed – hence this initiative.

C. Expert Consensus Aims

In recognizing the complex clinical challenges inherent to managing HF in the setting of multimorbidity and the role of expert guidelines in providing a comprehensive overview of the relative strengths and applicability of treatment options, the specific aims of this *Expert Consensus Statement* were two-fold:

1. To provide a comprehensive overview of the current literature focusing on the most common conditions requiring concurrent treatment and management in patients with HF.
2. To derive a practical set of recommendations for a systematic response to this increasingly common clinical phenomenon.

As such, we expect our pragmatic recommendations (from an international, multidisciplinary panel of health professionals with an ongoing interest and expertise in HF management) to complement contemporary guidelines to generate new initiatives to improve health outcomes in all affected individuals; regardless of the health care system in which they are managed.

D. Methods

We sought to derive a set of key recommendations (on a consensus basis) to guide future health policy and clinical practice in this area. Our recommendations are based on the following: **1**) an initial review of the literature identifying the ten most common conditions, other than hypertension and ischaemic heart disease, complicating the management of HF (anemia, arrhythmias, cognitive dysfunction, depression, diabetes, musculoskeletal disorders, renal dysfunction, respiratory disease, sleep disorders and thyroid disease), **2**) a systematic review of the published literature (2005 – 2015) describing HF and these ten conditions (178 published papers) and **3**) our expertise and experiences in managing complex patients with HF and multimorbidity.

E. Findings & Recommendations

Overall the published literature shows an increasing interest (both in volume and sophistication), but inherently fragmented approach to characterizing multimorbidity in HF. After carefully considering the available literature relative to our collective clinical experiences and practice and consistent with previous calls for a more systematic response to this growing clinical problem we made five key recommendations:

1. Multimorbidity in HF be recognized as a distinct clinical entity

As previously noted by Tinneti and colleagues (1), multimorbidity in HF has emerged as a distinct clinical entity associated with poor health outcomes and should be recognized as such to provoke a more systematic response. It is of particular concern that HF patients with a high burden of multimorbidity living in low-income areas are at increased risk of all-cause re-hospitalization: suggesting that illness burden influences the association between income and outcomes in these patients (2).

2. All patients hospitalized with HF should be routinely screened for multimorbidity

A logical extension to recognizing multimorbidity in HF as a distinct clinical entity is to identify which patients are affected. As such, we recommend all patients admitted to hospital with HF should be systematically screened for multimorbidity (full screening at least every 12 months if multiple admissions) in order to quantify the extent and nature of the problem. This should be noted in the clinical records as part of any communication to patient's wider health care team. It is important to note that any screening protocol will likely rely on a component of "routine" profiling, but also require an active component of profiling beyond current clinical practice (e.g. to determine cognitive function). **Table 1** summarizes the definitions and methods that could be routinely applied (with local adaptations) to identify the 10 most common comorbid conditions in HF.

Table 1: Routine Screening for multimorbidity in Heart Failure

Co-morbidity	Data source and determination	Definition / deficit threshold
Anemia	Full blood examination during hospital admission	Serum Hb level <130 (women) / <120 g/l (men) (3)
Atrial and ventricular arrhythmias	Review of medical notes with plus review of prescribed pharmacotherapy at discharge If high clinical suspicion of undiagnosed arrhythmia - 12-lead ECG, inpatient telemetry or extended ECG Holter monitoring	Confirmation of AF, other atrial arrhythmias, 2nd or 3r degree heart block, VT/VF with prescription of anti-arrhythmic therapy or pacemaker/ defibrillator device (4)
Cognitive impairment/ dementia	Assessed via Montreal Cognitive Assessment (MoCA) tool prior to hospital discharge by trained personnel	MoCA score < 26 out of a maximal possible score of 30. (5)
Depression/Anxiety	Assessed via PQ-2 (6) questionnaire prior to hospital discharge by trained personnel plus review of medical notes and prescribed pharmacotherapy at discharge. If positive, apply more comprehensive tool (e.g. HADS) (7)	Positive response to depressive symptoms and/or confirmed diagnosis (with active anti-depressive/anxiolytic) of depression or anxiety
Diabetes and metabolic disorders	Review of medical notes and prescribed pharmacotherapy at discharge Calculation of body mass index If high clinical suspicion of underlying diabetes HbA1c and/or glucose tolerance tests	Documented diagnosis of Type 2 Diabetes or obesity BMI > 30kg/m^2 plus dyslipidemia and/or hypertension (metabolic syndrome)
Musculoskeletal disorders	Review of medical notes and prescribed pharmacotherapy at discharge Frailty test with hand-grip manometer (8)	Documented diagnosis of arthritis, osteoporosis, gout or any other musculoskeletal condition requiring active therapy (e.g. anti-inflammatory or analgesia) This could be achieved by obtaining blood tests in addition to whole body scans via dual X-ray absorptiometry (DXA)
Renal impairment	Electrolytes and renal function obtained during hospital admission Calculation of body mass index	Estimated glomerular filtration rate < 60 mL/min/1.73m^2 (9)
Respiratory disease	Review of medical notes and prescribed pharmacotherapy at discharge If high clinical suspicion of underlying respiratory disease – formal lung function tests	Lung function confirmation of COPD, asthma and/or other chronic pulmonary condition requiring active treatment (10)
Thyroid disease	Review of medical notes and prescribed pharmacotherapy at discharge If high clinical suspicion of, or historical lack of screening, perform thyroid function tests (including thyroid stimulating hormone levels) at hospital admission	Documented hyper/ hypothyroidism based on according to national standards with associated anti-thyroid or thyroxine replacement therapy (11)
Sleep disorders	Review of medical notes and prescribed sleep support device. If high clinical suspicion of sleep disordered breathing perform formal sleep studies Use of a screening questionnaire in hospital to identify those with sleep-disordered breathing (12)	Documented diagnosis of obstructive or central sleep disordered breathing

3. Based on the extent/complexity of multimorbidity a list of individualized clinical priorities and goals be established

There are potentially many competing priorities arising from multimorbidity in HF that are not easily addressed in a generic manner – hence the historical difficulty for expert guideline committees to provide specific recommendations in the setting of marginal benefit-risk ratios. For example, there has been a traditional reluctance to apply high doses of neurohormonal/vasodilator therapy in the setting of frailty and high risk of falls and/or evidence of progressive renal dysfunction; despite the potential benefits overall (13, 14). It is on this basis that we recommend that in considering the nature and level of multimorbidity a formal list of clinical priorities should be considered by the treating physician and wider multidisciplinary team with

consideration of the need for specialist opinion for particularly difficult conditions, patient preferences and goals (15) and conflicting/contraindicated treatment options based on the same (see **Table 2**).

4. Individualized, home-based, multidisciplinary, case management be strongly considered to supplement standard HF management

As recently articulated in the AHA/ACC/HHS Strategies to Enhance Application of Clinical Practice Guidelines in Patients with Cardiovascular Disease and Comorbid Conditions (16), there is increasing imperative to adjust management strategies towards multimorbidity and standard HF management are no exception. Beyond recognizing and counting any particular problem (see recommendations 1-3), strategic plans that are robust (in most health care systems), flexible, workable and cost-effective to address that problem need to be formulated. Beyond summarizing the literature, this forms the major component on this Expert Consensus Statement. Unfortunately, despite the frequency of multimorbidity in HF, interventions applicable to these patients are scarce and to our knowledge there is no definitive approach to improve typically poor health outcomes over above standard HF management models of care. The inherent complexity of managing multiple comorbid conditions is exacerbated by issues such as frailty, social isolation, impaired cognition and limited income that frequently accompanies sufferers of HF, who are typically elderly (17-19) Interventions addressing multimorbidity and clinical complexity in this population have the potential to reduce hospitalizations and prolong survival beyond that achieved by traditional disease management programs or transitional care; particularly targeting residually poor communication and poorly coordinated transitions during hospital discharge between health care providers that contributes to negative health outcomes and increased financial burden on the healthcare system. However, new research to fully harness the potential of outreach models of care with case-management and empowering patients and their carers to prioritise and address potentially conflicting clinical and personal goals is urgently required.

5. Evaluation of outcomes in HF and multimorbidity should extend well beyond the short-term and encompass all-cause events and person-centered perspective

Despite an understandable focus on immediate and costly rebounds to hospital in the short-term (i.e. within 30-days) (20-23), there is a strong rationale for adopting a longer and more holistic perspective to reflect the entire patient journey for those with HF and multimorbidity. The classical description and understanding of the natural history of HF reinforces this point; noting how periods of clinical instability in those affected by HF typically correlate with recurrent periods of hospital stay (24). However, a good proportion of individuals with HF may spend a reasonably extended period of time in a relatively stable phase once their most immediate clinical issues are resolved.

F. Summary Conclusions

Multimorbidity and HF represents a growing health threat from the societal to individual perspective. Current health care strategies need to be adapted (as per our five key recommendations) to improve typically poor health outcomes in this clinical setting. Figure 1 shows how are recommendations might be easily applied in the clinical setting.

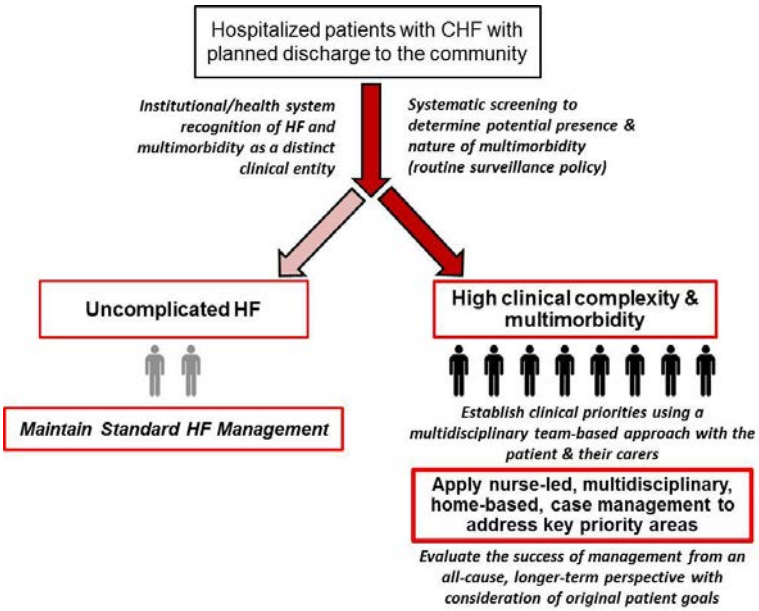

Figure 1: Putting the five key recommendations into practice

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Table 2: Summary of the literature most relevant to the concurrent management of HF and the ten pre-specified concurrent conditions

Co-morbidity	Prevalence & Impact on heart failure (HF)	Management Options	Clinical Caveats & Considerations
Anemia and reduced hemoglobin (Hb) levels	• Commonly reported in HF (1-3); occurs in 20-30% of patients with the syndrome • Low Hb levels are associated with HF-related fatigue (comparable to cancer-related fatigue) (4, 5) • Correlated with increases in mortality and morbidity (1, 6, 7) • It is unclear whether anemia is a cause or a consequence of the low-output HF and its etiology is multifactorial (8, 9) • Risk factor for development of HF (10) • Iron deficiency is a valid independent therapeutic target (11). It is common in CHF in both those who are anemic and non-anemic. • Iron deficiency is more commonly found in non-anemic women with CHF than non-anemic men with CHF (12, 13) • Anemia is associated with increased risk of hospitalization (3) • There are no generally accepted guidelines regarding the treatment of anemia in CHF (3).	• Increase Hb levels via erythropoietin (14) • Clinical practice guidelines (American College of Physicians) suggest using erythropoiesis-stimulating agents to increase Hb level in patients with mild to moderate anemia with acute heart failure or coronary heart disease (15) but it is not recommended for routine use in those with chronic heart failure (16) • Intravenous ferric carboxymaltose-improves symptoms, functional capacity, and quality of life (QoL) in stable, symptomatic, ambulatory patients with the syndrome (11) • Intravenous (IV) iron is superior to oral iron in improving functional capacity of CHF patients. Both IV and oral iron is effective in correcting anemia (IRON-HF RCT) (6) • Iron replacement therapy (oral or IV) improves QoL, exercise capacity (6MWT) (17), and reduces hospitalizations overall (3) • Iron status needs to be routinely monitored in patients with the syndrome and in particular those who are re-hospitalized for worsening HF (12, 18) • New onset anemia is common in CHF patients. Over time this relates to increased mortality and morbidity. Routine monitoring of iron levels in this population is advised (19)	• Increasing Hb levels via erythropoietin treatment has been associated with excessive vascular events • Oral and intravenous ferric carboxymaltose therapy (11) is safe, well-tolerated and has no adverse side effects but more trials assessing this are required (3, 11) • There is mixed evidence on the use of Darbepoetin Alfa for treatment of anemia in those with HFrEF (i.e. systolic dysfunction) and moderate anemia. Some studies report it does not improve clinical outcomes in this clinical setting (13, 14, 20) and others report improvement in Hb levels with no adverse effects (21-23) • Red blood cell (RBC) transfusion in patients with acute coronary syndrome (ACS) significantly increases risk of mortality and is not recommended as a safe form of treatment (24)
Atrial and ventricular arrhythmias	• Atrial fibrillation (AF) and HF share common risk factors, often coexist (up to 50% depending on the patient's age and clinical profile), and confer additive adverse effects	• Beta-blockers and/or digoxin are the drugs of choice for rate control in patients with concomitant HF and AF because of their known benefits in HF (27, 28)	• Some studies have failed to demonstrate a benefit of beta-blockade in HF patients who also have AF (31, 32) (A treatment-

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	when occurring simultaneously (25, 26) • Patients with AF exhibit increased risk of mortality due to HF and stroke (25) • Ventricular arrhythmias (VAs) are frequent in HF patients, particularly in those with a dilated LV and reduced LVEF (27).	• Anti-arrhythmic drugs are the first-line rhythm control option for AF (but see cautions) (29) • In patients who fail pharmacologic rate control, atrioventricular node ablation and ventricular pacing can be attempted (30) • For rhythm control, immediate electrical cardioversion is recommended for HF patients with new-onset AF when pharmacological measures have failed (27)	induced decline in BP of > 10 mmHg may adversely affect cardiac function in HF patients, offsetting the benefits of rate control (32)) • HF patients are at increased risk of adverse effects from antiarrhythmic drugs, and the agents available to maintain sinus rhythm are limited in the presence of HF (33-35) • Amiodarone and dofetilide are the only guideline-recommended antiarrhythmic agents for this patient population (36) However…. • Their use is limited by significant drug–drug interactions and adverse effects (37) • Long-term use of amiodarone carries risks of significant pulmonary, hepatic, and thyroid toxicity and is associated with symptomatic bradycardia requiring pacemaker implantation (37) • Dronedarone is contraindicated in HF as it is associated with an increased mortality in patients with HF NYHA class IV and NYHA classes II-III (38) • Flecainide may increase the risk of ventricular arrhythmias in impaired left ventricular function and may worsen HF (39) • Ablation and pacing are an effective method to achieve rate control, but prolonged right ventricular pacing may worsen HF (30)
Cognitive	• 30% to 80% of patients with HF experience	• ACE inhibitors, cardiotonic medication	• No reported contraindications or

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impairment/ dementia	some degree of cognitive impairment (CI) (40, 41) • The etiology of CI is heterogeneous and it can be promoted or caused by numerous somatic factors. Relevant somatic factors include hypertension, diabetes mellitus, heart failure, chronic obstructive airways disease and bronchial asthma. Cognitive impairment may be facilitated by hypercholesterolemia, chronic renal failure, and hypothyroidism (42, 43) • The severity of CI parallels that of CHF (44) • HF patients with severe forms of CI are older, have less formal education and have significantly more comorbidities. For example, depressed patients have twice the odds of being impaired in the cognitive domains of executive function, processing speed, and memory (odds ratio 1.98, 95% CI 1.08-3.64) (45) • HF negatively impacts multiple aspects of cognitive functioning, including attention, working memory, learning ability and delay recall, executive function, and psychomotor speed (40, 41, 46) • Higher BMI is associated with CI in those with HF. Particular, declines in attention and executive functioning in men but not women (47) • Mild CI lowers self-efficacy in self-care management (48) • HF patients with CI fail to recognize early symptoms and make appropriate self-care decisions (49), have difficulty with adherence to medication management (44, 50), and are	(such as digoxin), and antiarrhythmic drugs improve cognitive performance (54) • Physical activity positively impacts upon cognitive performance (55) • Structured cognitive training programs have been shown to improve working and general memory, psychomotor speed, executive function (56) • Cardiac resynchronization therapy produces significant short-term improvements in executive and visuospatial functioning (57) • Cardiac resynchronization therapy has also been shown to improve neurocognitive (attention, information processing, and controlled oral word processing), and psychosocial functioning in patients by increasing cardiac output and cerebral perfusion. However, further testing is required as this study was comprised of a small sample (n=20) (58) • Enhanced external counter-pulsation therapy significantly improves cognitive domains including spontaneous naming, attention, and executive functioning (59) • A nurse-based outpatient clinic Intervention led to significant improvements on the Mini-Mental Status tool in females with HF at 6-months when compared to standard care (60)	side effects of any of the interventions outlined to the left - with the exception of reduced adherence over time (54, 55, 57, 61)

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	less likely to participate in outpatient treatment programs resulting in worse clinical outcomes (51) • These patients are at increased risk of HF decompensation, unplanned hospital admissions and mortality (52) • CI is associated with a six fold increase in functional disability (OR: 6.49; 95% C.I. 4.39–9.59) independently of potential confounders including age, sex, hypotension, comorbidities and medication (53)		
Diabetes (Type 2) and other related conditions including obesity/ metabolic syndrome	• Type 2 diabetes is a common co-morbidity in HF and the two diseases are interrelated (62, 63) • Approx. 1/3 of patients with HF have Type 2 Diabetes (63) • According to the most recent evidence, the prevalence of comorbid HF among those with diabetes in individuals older than 65 is 1.5%-2%. Moreover, this is expected to increase exponentially in the next decades (64) • Diabetes is associated with higher risks for both all-cause and HF-related preventable hospitalizations and rehospitalizations (65) • The presence of HF in patients with diabetes confers a 10-fold increase in mortality and a 5-year survival rate of only 12.5% (66) • The risk of mortality is the same for both ischemic (HFrEF) and non-ischemic (typically HFpEF) patients with HF (67)	• Metformin is the first-line agent for treating Type 2 diabetes in the setting of HF (68) ○ Metformin improves insulin sensitivity by enhancing peripheral glucose uptake and reducing hepatic glucose production (68) ○ Associated with lower mortality and rehospitalization (69-72) ○ Has been associated with reducing MI size in patients presenting with STEMI (73) • Sulphonylureas can also be used and pose no increased mortality risk to HF patients (74) • There is controversy in the literature pertaining to the use of thiazolidinedione (TZD), an insulin-sensitizing medication in those with DM & HF. One study has reported that TZDs was not associated with an increased risk of HF hospitalization or total mortality when compared with those not receiving insulin-sensitizing medications (75), whereas others have reported safety concerns (76)	• Metformin poses a risk of lactic acidosis but can be safely used in patients with normal renal function, stable hemodynamics, and mild-moderate LV dysfunction (68, 81) • Thiazolidinediones should not cautiously in those with symptomatic HF as they cause fluid retention and increase hospitalization (63, 72) • Sulphonylureas increase BMI (74) • The use of insulin in HF is controversial – tight glycemic control improves survival in advanced HF, but overall, insulin-treated HF patients have significantly worse prognosis (82) • In addition, insulin increases BMI (82) • Use of saxagliptin [selective dipeptidyl peptidase-4 (DPP-4)] inhibitor confers no overall benefit when compared to placebo and associated with a higher risk of hospitalization for HF when followed-up over 2-years (83, 84) • A trend towards increased risk of

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		• Ramipril, an ACE inhibitor is safe to use over the long-term in HF patients with diabetes (77). • Glitazones (eg rosiglitazone and Pioglitazone) may also be prescribed ○ However, the uses of pioglitazone to treat diabetes in those with CVD have shown mixed results. One study reported that this drug has good long-term tolerability with low adverse effects (78), however others have reported pioglitazone induced significant increases in natriuretic peptides and alterations of cardiac size (79) and increased hospitalizations (Giles 2008) ○ Rosiglitazone has been recommended over pioglitazone to improve myocardial systolic function (80)	hospital admissions for HF [relative risk (RR) 1.30, 95% CI 0.35–4.82] and all-cause mortality (HR 1.50, 95% CI 0.49–4.59) has been associated with rosiglitazone treatment (85), however more long-term studies are required. One 52-week, long-term study found that rosiglitazone improved glycemic control and did not adversely affect LVEF in patients with CHF (86) • Pioglitazone is associated with a higher rate of HF hospitalizations (87)
Musculoskeletal disorders	• Musculoskeletal disorders such as osteoporosis and osteopenia, osteoarthritis (OA), and rheumatoid arthritis (RA) are common comorbidities in patients with HF, particularly due to the increased prevalence of both in older populations • Mortality at 1 year following HF is higher in those with RA when compared to those without RA (35% versus 19%; multivariable hazard ratio 1.89, 95% confidence interval 1.26-2.84) (88) • Severe functional disability/frailty is present in >50% of patients admitted to hospital for HF (89) • Pre-admission functional status is a predictor of short-term mortality in those with HF (89) • Frailty occurs in 15-74% of HF patients	• Optimal treatment of CHF with osteoporosis is to increase vitamin D, calcium and improve physical activity levels (91) • Topical non-steroidal creams, capsaicin, topical lidocaine, intra-articular therapies, and judicious use of narcotics are also advocated as they do not negatively impact on HF (98) • Osteopenia and osteoporosis in HF should be managed with a combination of vitamin D and calcium supplementation, bisphosphonates, and non-aerobic weight-bearing exercises (94)	• Avoid use of NSAIDs wherever possible due to risk of sodium and water retention, peripheral vasoconstriction and increased severity of HF (99) • When NSAIDs are used, naproxen is preferred; avoid ibuprofen due to its blood-thinning properties and the increased risk of cardiovascular events (100, 101) • Patients taking ≥ 2 anti-inflammatories were found to have of N-terminal pro-B-type natriuretic peptide values of ≥ 100 ng/L (NT-proBNP). This is significantly associated with a 3.7-fold higher

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	(depending on the study population and assessment method(s) (90) • Those with HF have lower bone mineral density-Z (BMD-Z) scores. HF patients also have lower vitamin D levels and physical performance scores, and higher fragility marker scores and inflammatory markers (TNF-α) (91) • There is a significant association between fragility marker scores and ejection fraction (91) • HF is associated with a 30% increase in fractures independent of risk factors associated with BMD (92, 93) • Increased bone resorption due to renal insufficiency with consecutive secondary hyperparathyroidism are the main causes for BMD loss in CHF (94) • Among hip fracture patients, the main risk factors for in-hospital mortality were advancing age, male gender, HF and liver disease (95) • Among hip and knee OA patients, severity of OA disability is associated with a significant increase in all-cause mortality and serious CVD adverse events after controlling for multiple confounders (96) • AMI patients with RA receiving similar treatment with reperfusion therapy and cardio protective medications were found to have similar short-term outcomes compared to patients without RA. AMI patients with RA, however, had poorer long-term outcomes which included mortality and recurrent MI (97)		risk for cardiovascular-related adverse events (102-104). Patients with a NT-proBNP level below 100 pg/ml had a 0.94% rate of thrombotic events or HF at 2 years (104) • Corticosteroids should also be used with caution as they can worsen HF via sodium and water retention (39, 105) • At high doses, corticosteroids may also cause arrhythmias(106) • TNF antagonists (e.g. infliximab, etanercept) should be avoided in RA patients with HF as it increases LVEF (107) and increases BP levels (108) • A 2011 systematic review (n=20 articles) has found that TNF antagonists do not increase the risk of HF (109)

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Co-morbidity	**Prevalence & Impact on heart failure (HF)**	**Management Options**	**Clinical Caveats & Considerations**
Renal impairment/disease	• Renal dysfunction is present in 35–50% of CHF patients and is often chronic in nature (110) • It is consistently an independent marker of adverse outcome in HF (110, 111) • HF mortality is significantly higher in patients with baseline renal impairment (RI) (112, 113) • Renal impairment can range from reversible ischemic damage to renal failure requiring short- or long-term renal replacement therapy (114)	• Clinical guidelines routinely recommend the use of ACE inhibitors or ARBs to treat patients with comorbid renal and cardiac diseases (115) • The ARB valsartan effectively reduces glomerular filtration rate and morbidity in those with HF and Chronic Kidney Disease (CKD)-The Valsartan in Heart Failure RCT (Val-HeFT) (116) • Beta blockers provide benefits in HF and renal dysfunction with no contraindications (117) • Vasopressin antagonists may improve fluid retention, hyponatremia and renal dysfunction in HF, but further research is needed into long-term benefits and contraindications (118) • There is limited evidence regarding the benefits of Implantable Cardioverter Defibrillator (ICD) therapy for patients with HF and renal dysfunction, but there do not appear to be contraindications (119, 120) • Cardiac resynchronization therapy may provide the largest survival benefit in HF patients with moderate renal impairment by improving glomerular filtration rate and left ventricular function (121) • A recent systematic review revealed that resynchronization therapy increased survival rates in patients with CHF and chronic kidney disease, compared with other modalities of treatment (medical therapy or ICD alone) (122)	• ACE inhibitors and ARBs are contraindicated in patients with a history of angioedema (126). • If renal function deteriorates to a significant degree (e.g. 25% increase in serum creatinine or 15% decrease in eGFR), the risk benefit effect of treatment should be reevaluated (127) • Valsartan is safe and well-tolerated in those with stable to moderate HF (116, 128) • Nesiritide should not be used in patients with concurrent renal impairment as it is associated with an increased risk of mortality (129)

Table 2: Summary of the literature most relevant to the concurrent management of HF and the ten pre-specified concurrent conditions			
Co-morbidity	**Prevalence & Impact on heart failure (HF)**	**Management Options**	**Clinical Caveats & Considerations**
		• Levosimendan has been shown to have an immediate reno-protective effect in patients with HF. This is mediated by an increase in renal blood flow, due to a selective renal arterial and venous vasodilating action (123, 124) • In HF with reduced ejection fraction (EF), renin–angiotensin receptor (RAS) antagonists reduced mortality. In 602 elderly patients RAS antagonist use was associated with 55% [95%confidence interval (CI) 51–59] vs. 45%(41–49) 1-year survival, P= 0.001, with a hazard ratio (HR) for mortality of 0.76 (95% CI 0.67–0.86, P=0.001) (125)	
Respiratory disease/dyspnea	• Dyspnea is a key primary symptom and clinical trial endpoint in acute HF, yet objective assessment is lacking (130) • Dyspnea is difficult to measure in clinical trials due to its subjective nature and the absence of a validated, gold standard assessment tool (130) • Patients with dyspnea and HF are extremely physically inactive and are even unable to perform an exercise test. They are at a greater risk of poorer clinical outcomes and mortality (131) • Up to one third of HF outpatients have comorbid chronic obstructive pulmonary disease (COPD) (132) • The symptoms of HF and COPD overlap significantly to the extent that the two disorders are difficult to distinguish symptomatically (133)	• Sildenafil may be useful for dyspnoea in CHF due to reduction of peripheral muscle signalling (134) • Some evidence supports the use of exercise training and mindfulness-based programs for dyspnea in HF (134) • Bronchodilators (a first-line COPD treatment) have not been systematically evaluated in HF (due to exclusion of HF patients from RCTs), so although there is no evidence for contraindication, anticholinergics are the preferred option until further evidence is obtained (135) • In HF patients with COPD, a long-acting anticholinergic is recommended (135) • Inhaled steroids are also effective and safe for COPD in HF patients (135) • Bilevel positive airway pressure ventilation improved outcomes (re-hospitalizations and mortality) in those with COPD and acute	• Oral steroids can cause sodium and fluid retention and thus should be used with caution for COPD in HF patients (135) • Bronchodilator is not recommended for non-COPD dyspnoea in acute heart failure as it has been associated with worse clinical outcomes(139) • IV furosemide is safe and effective for use in CHF patients (137) • Bilevel positive airway pressure ventilation is non-invasive and well-tolerated in HF patients with COPD (136)

Table 2: Summary of the literature most relevant to the concurrent management of HF and the ten pre-specified concurrent conditions			
Co-morbidity	**Prevalence & Impact on heart failure (HF)**	**Management Options**	**Clinical Caveats & Considerations**
		decompensated HF (136) • IV furosemide (diuretic treatment) administered over a 3-day period in hospitalized CHF patients is effective in significantly reducing fluid, improving breathlessness and reducing re-hospitalizations (137) • Oxygen therapy is no more effective than normal breathing in those with dyspnea and cardiac conditions (138)	
Sleep disordered breathing (obstructive and/or central sleep apnea)	• Common in both predominant forms HF (140) -[HFrEF (140) and HFpEF (141)] • Comorbid sleep-disordered breathing may take the form of either Obstructive sleep apnea (OSA) or Cheyne-Stokes respiration-central sleep apnea (CSA) and is frequently accompanied by a poor prognosis (142-145) • OSA is an independent risk factor for hypertension, CHF, and pulmonary hypertension (142, 145) • Patients with CSA have advanced symptoms and more impaired cardiovascular function than those without central sleep apnea (141) • CSA affects CV function adversely by causing tissue hypoxia, arousals from sleep, and activation of the sympathetic nervous system • CSA independently increases the risk of death (146) • Sleep disordered breathing may contribute to disease progression (147)	• Cardioverter-defibrillator therapies (140) • Continuous positive airway pressure (CPAP) therapy (143, 148) is associated with: ○ Improved nocturnal oxygenation ○ Increased LVEF (only when the treatment reduces the apnea–hypopnea index), ○ Lower norepinephrine levels ○ Increases exercise capacity (6MWT) (149) ○ Reduces systolic blood pressure ○ Improved left ventricular systolic function (150) ○ Reduced hospital readmission and ED visits 30 days after discharge (151) • CPAP does not impact on survival rates (149) • Surgical valve repair improves cardiac function and CSA (152) • Auto-servoventilation (ASV) has been found to significantly improve CSA to a greater extent than CPAP in those with HF (153-160)	• No adverse side effects (147, 160) • Poor patient tolerability (147) • Poor patient compliance (147) • The SERVE-HF trial, a multinational, multicentre, randomized, parallel trial designed to assess the effects of addition of Adaptive servo-ventilation (PaceWave™, AutoSet CS™; ResMed) for the treatment of sleep apnoea in those with HF. This trial was found to increase mortality in those with symptomatic HF (165)

Table 2: Summary of the literature most relevant to the concurrent management of HF and the ten pre-specified concurrent conditions			
Co-morbidity	**Prevalence & Impact on heart failure (HF)**	**Management Options**	**Clinical Caveats & Considerations**
		• Auto-servoventilation acts as an anti-inflammatory and is an important contributor to reductions in cardiac events (161) • Randomized studies with large sample sizes evaluating non-pharmacological nursing interventions that improve sleep are required (162) • Biventricular stimulation decreases central sleep apnea and improves quality of sleep and daytime sleepiness in patients with CHF (163) • A 6-monoth aerobic exercise program improved sleep apnea in patients with CHF (164)	
Thyroid Disease	• Untreated overt hyperthyroidism and hypothyroidism have been reported as common causes of HF (166) • Recent estimates suggest that approximately 10% of HF patients have comorbid thyroid disease (167) • Hypothyroidism is more prevalent in men than women (168) • Thyroid dysfunction is a key risk factor for HF development (169) • A retrospective study (1969-2002) with a mean 9-year follow-up found that the rate of cardiovascular-related hospitalizations were significantly higher in those with hyperthyroidism when compared to controls [637.1 vs. 476.4 per 10 000 person-years, rate ratio (RR) 1.12, 95% confidence interval (CI) 1.03-1.21 (170)	• Treatment with levothyroxine normalizes TSH levels (169) • Treatment with replacement doses of L-T4 reduces myocyte apoptosis and improves cardiovascular performance in mild and subclinical hypothyroidism (173) • Definitive treatment of hyperthyroidism with anti-thyroid drugs (I-radioiodineis) usually recommended to recover cardiac function (174) • Some studies suggest that replacement doses of triiodothyronine (T3) may improve cardiovascular remodeling and function in patients with HF and low T3 syndrome (173) • Treatment with β-adrenergic blockade is first-line therapy to reduce heart rate in cardio-toxic thyroid patients (174) • In thyroid patients with overt heart failure	• I-radioiodine is both safe and effective especially when used in conjunction with β-adrenergic blockade (177) • However, a trend towards increased cardiac mortality has been reported in treated hyperthyroid patients (178)

Table 2: Summary of the literature most relevant to the concurrent management of HF and the ten pre-specified concurrent conditions			
Co-morbidity	**Prevalence & Impact on heart failure (HF)**	**Management Options**	**Clinical Caveats & Considerations**
	• Surgically treated hyperthyroidism still increases the risk of hospitalization due to CVD (up to 2 decades after effective surgical treatment) (171) • Thyroid Stimulating Hormone (TSH) levels above normal are independently associated with increased mortality and cardiac-related hospitalizations (169) • Risks for cardiac events in HF patients are increased with both low and high levels of TSH TSH ≥10 and <0.10 mIU/L (172)	involving pulmonary congestion, treatment with digitalis and diuretics is appropriate (175) • Radioactive Iodine for hyperthyroidism increases the risk of cardiovascular related morbidity and this risk lasts up to 35-years (170) • Cardiac resynchronization therapy (CRT) is associated with a worse prognosis of hypothyroidism (176)	

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