

## REVIEW ARTICLE

# Common Comorbidities that Alter Heart Failure Prognosis - Shaping New Thinking for Practice

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**Abstract:** At least half of all heart failure (CHF) patients will have a comorbidity that could be undertreated, requires additional speciality input and/or polypharmacy. These patients are then at risk of iatrogenic and disease-related complications and readmissions if not closely supervised. Common comorbidities of relevance are cardiorenal and cardiometabolic syndromes (DM, obesity, OS-A), chronic airways disease, elderly age, and accompanying pharmacotherapies. The structure of community practice often leaves primary, speciality, and allied health care in silos. For example, cardiology speciality training in Australia creates excellent sub-specialists to deliver diagnostic and therapeutic advances. A casualty of this process has been the gradual alienation of general cardiology toward general internal medical specialists and primary care practitioners. The consequences are largely noticed in community practice. The issue is compounded by suboptimal communication of information. This review explores these issues from a cardiology sub-speciality lens; firstly cross speciality areas that are important for cardiologists to maintain their skill, and finally, to obtain a brief overview of disease management and identify game-changing common denominators such as endothelial dysfunction and self-management.

## ARTICLE HISTORY

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## 1. INTRODUCTION

Congestive Heart Failure (CHF) is an epidemic that will contribute to deteriorating health budgets. At this point, optimal care, defined as delivering guideline-based care through a heart failure (CHF) program, is not achieved mainly due to the ground (local) factors and inability to match those differences with service capacity. The OPTIMIZE-HF study proves that a standardised process of care may be all that is needed to achieve this and reduce the significant morbidity and mortality, approaching 50% at 5 years [1, 2]. Equally important is the evolving paradigm of Diastolic Heart Failure (DHF) syndrome that appears in older patients with similarly poor outcomes [3].

The spectrum of CHF several decades ago and the requirements of practice are changing in many directions. While this may not adversely impact health outcomes in most health clusters, it is gradually changing cost-efficacy in

an unhealthy direction. Eventually, parity of services from the funding will decline, and this could influence health outcomes. For example, in CHF alone, more than 50% of patients will have at least one comorbidity such as diabetes, obesity and metabolic syndromes, renal impairment, chronic obstructive lung diseases, and other aging-associated factors. Many of these conditions now require multidisciplinary care, including non-cardiac specialists and allied health practitioners. Very importantly, it is not possible to improve cardiac prognosis without addressing them [4, 5].

This review has several broad aims in the context of cost-efficacy: firstly, we explore, through a cardiology lens, several common co-morbidities associated with CHF that influences all major adverse cardiovascular outcomes (MACE) and challenges; secondly, we look at disease management questions. The specifics are listed:

[i] Comorbidities:

- [a] What are priority areas and their common denominators?
- [b] What are the boundaries of cross speciality

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- clinical practice and referrals?  
 [c] What are the parameters for clinical information from research collaborations and *vice versa*?

[ii] Disease Management:

- [a] What are suitable mechanisms for training and regulatory authorities to obtain information on cost-efficacy from health clusters in real-time, with continuity?  
 [b] Where are the benefits of self-management efficacy and endothelial dysfunction analysis for monitoring and reducing MACE?  
 [c] Is readmission an important/ sufficient MACE parameter for phase - 4 trials?

## 1.1. CardioRenal Syndrome

### 1.1.1. Clinical Summary

ADHERE, OPTIMIZE-HF and EURO-HF were three large registries that helped identify the depth and significance of all stages of renal impairment and adverse major cardiovascular outcomes (MACE). The cardiovascular system maintains direct communication with all major organ systems; however, the cardiorenal interaction appears the most substantial in pathophysiological terms. The American National Kidney Foundation Task Force on cardiovascular outcomes in CKD considered renal diseases as the “highest risk group” for future cardiovascular events and appropriately risk stratification and treatments for this risk be appropriately factored into guidelines. Further studies consolidated this knowledge and highlighted therapeutic under prescription and even outright lack of prospective data (Table 1) [6]. The literature highlights three viewpoints: the renal perspective, the cardiac perspective, and, lastly, the issue of therapeutics. Both renal and cardiac impairment are associated with and contribute to disease in the other acutely and chronically. Acute worsening of cardiac and renal function portends a worse prognosis, particularly during admissions. The ethology and risk factors are multifactorial with significant overlap [7].

### 1.1.2. What Cardiologist’s Need to Know

The diagnosis for renal impairment is principally by detecting proteinuria in the urine (early) or increasing blood Serum Creatinine (SCr) and reducing estimated Glomerular Filtration Rates (eGFR). eGFR tends to decline naturally with age, comorbidities, and medication use. A sizeable CHF population will have at least some degree of renal impairment at baseline and greater when associated with specific comorbidities. These patients are then at risk of undertreatment, adverse cardiorenal syndrome crosstalk, and hospital deterioration. In the acute setting, the SCr rise is delayed by more than 48 hours with renal injury, while the eGFR values will not accurately reflect true renal function. Numerous biomarkers have been trialled, not meeting clinical bedside translation standards. In pathophysiological terms (excluding direct toxins), determining the main determinant of a sin-

gle nephron GFR will help ( $SNGFR = kf \times \Delta P$ ). Renal perfusion *via* afferent and efferent arterioles can be altered by pre-renal hypoperfusion, renal (intraglomerular hypertension) and relative post renal hypertension, and creating poor transglomerular pressures. Prescribing can be challenging when renal function is poor, and haemodynamics are low [8]. It is important, however, to set actionable clinical goals, and the four important ones are as follows: 1. Maintaining good pre-renal perfusion and transglomerular pressures for blood to flow across efferent arterioles; 2. Monitoring to reflect acuity; 3. Medication - start medication low and slow. It is always better to have some medication than none; 4. Medical case manager - either GP or specialist should be appointed to lead the multidisciplinary team and be the go-to person for issues.

### 1.1.3. Future Considerations

Cardiorenal syndrome requires guidelines to help steer an individual approach where needed [10]. As venturing into variations could lead to biases, this is preferably done within a team-based approach. Other areas to explore are as follows: 1. Documenting perfusion *versus* Nephron issues adequately; 2. Creating a multidisciplinary team; 3. Improved diagnostics options for diagnosis and monitoring; 4. Improved renal injury markers; 5. Increasing indications for therapies, *e.g.*, Entresto; SGLT-2i; 6. Incorporating prescribing into guidelines.

## 2. OBESITY AND ASSOCIATED SYNDROMES (METABOLICALLY HEALTHY OBESITY)

### 2.1. Clinical Summary

Obesity is an epidemic that does not hide, presenting in teenage years. Its chronicity is seen as waves in the health system across all demographic spectra. The evidence for association with CVD is also good evidence for atherosclerosis, hypercholesterolemia (high LDL cholesterol and low HDL), hypertension and Type 2 diabetes (especially central adiposity); ischemic heart disease, CVD incidence in young to middle-aged adults, Coronary Heart Disease (CHD) incidence in adults. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) estimated that > 2.6 million (21% over 25 years) were obese (BMI  $\geq$  30), double the rate from 1980. Lower socioeconomic status and Aboriginal and Torres Strait Islander peoples are at greater risk [10].

### 2.2. What Cardiologist’s Need to Know

Obesity is encountered in a high percentage of cardiology consults and has many faces. Firstly it is a disease that contributes to morbidity and mortality. This morbidity and mortality have paradoxes within associated cardiovascular conditions such as heart failure. It is a syndrome that has taken a generic label and requires individualisation, *e.g.*, sociological and genetic (ethnic) factors play important roles. There are subcategories such as ‘Metabolically healthy obesity’ if followed for more than 10 years also reveals previously unidentified risks [11]. HF specifically, Framingham Heart Study noted every one unit increment in BMI increa-

**Table 1. Comorbidity, risks and future considerations.**

Reference	Prevalence	Outcomes	Model of Care	Future Considerations
CRI [6]	<ul style="list-style-type: none"> <li>eGFR: &gt;60 (1.0%); 45-59 (5.2%); 30-44 (12.6%); 15-29 (20.8%); &lt;15 (18.5%)</li> <li>ADHF - 63.6% eGFR &lt;30-45 ml/m min/1.73 m<sup>2</sup></li> <li>Underreporting of ↓ eGFR in ~ 50% admitted CHF</li> </ul>	<ul style="list-style-type: none"> <li>↓ eGFR independent predictor MACE &amp; ↑ LOH</li> <li>WRF predicts short term MACE</li> </ul>	<ol style="list-style-type: none"> <li>Co-shared, multidisciplinary               <ol style="list-style-type: none"> <li>eGFR &gt;60 GP lead</li> <li>eGFR &lt;45 Renal-Cardiology specialist co share.</li> </ol> </li> <li>Allied health priority if associated with MetS</li> </ol>	<ol style="list-style-type: none"> <li>Team Structure &amp; shared records:               <ul style="list-style-type: none"> <li>Medications - explore all prognostic medications. Document team decision if treatment withheld and circumstances to restart.                   <ul style="list-style-type: none"> <li>Convene team meeting - e.g., eGFR &lt;30, yearly</li> <li>Identify team lead</li> </ul> </li> </ul> </li> <li>Phase 4 study options for SGLT-2 &amp; ARNi</li> <li>Aggressive treatment for CRI aetiology</li> </ol>
Obesity Syndromes [10, 12, 16]	<ul style="list-style-type: none"> <li>Global 39% &lt;18yo ↑ weight; 13% obese</li> <li>↑ CVD: CAD, CHF, HT arrhythmia, SCD</li> <li>↑ Non-CVD - DM, OSA, MSS, in almost all other organ systems</li> </ul>	<ul style="list-style-type: none"> <li>↑ risk BMI &gt;35 kg/m<sup>2</sup></li> <li>↑ mortality BMI &gt;40&gt;35 kg/m<sup>2</sup></li> <li>Metabolically healthy obese ↑ risk (&gt;100%) when beyond 10yrs</li> </ul>	1. Co-shared, multidisciplinary	<ol style="list-style-type: none"> <li>Defining obesity risk for individuals</li> <li>Defining obesity targets for individuals</li> <li>Early use of SGLT-2 and ARNi</li> <li>Funding and models of care across the health spectrum</li> </ol>
Diabetes	<ul style="list-style-type: none"> <li>25 - 40% of HF</li> </ul>	<ul style="list-style-type: none"> <li>Median survival &lt;50% of non-diabetic HF</li> </ul>	1. Co-shared Multidisciplinary	<ol style="list-style-type: none"> <li>Phase 4 study options for SGLT-2 &amp; ARNi</li> <li>Co-shared models of care</li> </ol>
Elderly & Complex Care	<ul style="list-style-type: none"> <li>Mean age: 70 - 75 y (SD 15y).</li> <li>Prevalence: 1% - 2%; &lt;1% 40 y; 2× ↑ each decade, peak 10% &gt;75 yo. Lifetime risk 40 - 80 y is 40%.</li> <li>CV comorbidity: &gt;40%-70% HT, CRI, DM, IHD AF; OSA. &gt;25% have &gt;5 comorbidities.</li> <li>Non-CV: &gt;70% HF patients &gt;80 y vulnerable for "frailty".</li> <li>Acute HF admission &gt;50% elderly - mean age 75 yrs or octogenarian 80 years(range 21% to38%).</li> <li>Readmission: 3 - 6m disch 27% &amp; 47% (60/90 d to 1 y-30% and 32%); &gt;50% readmissions non-CV (50% medication, disability)</li> </ul>	<ul style="list-style-type: none"> <li>Mortality: 5-y mort 50%; mdn survival 4.2 y; &gt;65 yrs 30 d &amp; 12 mth 27.5%.</li> <li>Inpatient mortality 38%, 30 d &amp; 16.4% 12 mo.</li> <li>IH mortality-pneumonia (OR 1.60), WRF (1.48), ischemia (OR 1.20);</li> <li>Postdischarge mortality 60/90 d to 1 y-5.4% to 14% and 17.4%; ischemia/WRF (OR 1.52/ 1.46).</li> <li>IH: mLOS: 4 to 20 d; mortality 4% to 30%.</li> </ul>	<ol style="list-style-type: none"> <li>Co-shared cardiogeriatrics.</li> <li>Greater allied health support for cardiac and non-cardiac comorbidities.</li> <li>Coordinated home visits.</li> </ol>	<ol style="list-style-type: none"> <li>Cost-efficacy team               <ul style="list-style-type: none"> <li>decisions on device interventions.</li> <li>Medication review ongoing cost-benefit vs. QOL/ risk.</li> </ul> </li> <li>Model of care and funding - home visit; telehealth (social isolation).</li> </ol>

**Note:** Four important comorbidities are highlighted. All these comorbidities present as a syndrome, risk factors, and without directly addressing the disease pathophysiology, HF prognosis will remain suboptimal. These comorbidities all have overlapping etiologies and pathophysiology as well as disparate. Individualisation of care is thus vital. In the medicare funded model, the choices are limited. While they may work for the majority, patients can get left behind. (Fig. 2) and Table 2 draw attention to several areas to consider in newer models. Regardless, all models of care must have basic personnel or a 'health care team.' This team constitutes specialists, general practitioners, nursing, and allied health services. Identifying KPI that could make game-changing differences should be given priority, see (Fig. 3).

**Abbreviations:** ~ approximately; ↑ increase; ↓ decrease; ARNi - angiotensin receptor neprilysin inhibitor; CAD coronary artery disease; CHF - congestive heart failure; CRI - chronic renal insufficiency; eGFR - estimated glomerular filtration rate (ml/m min/1.73 m<sup>2</sup>); GP - general practitioner; HT - hypertension; LOH - length of hospitalisation; MACE - major adverse cardiovascular outcomes; MetS - metabolic syndrome; MSS - musculoskeletal and rheumatological; Ref - references; SCD - sudden cardiac death; WRF - worsening renal function.

sed risk 5-7% for men and women, respectively. In chronic and acute decompensated HF, an obesity paradox was noted with lower (BMI < 27.8 kg/m<sup>2</sup>) and normal BMI; however, its association with generic CHF, ischemic or other causes remains unclear [12-15].

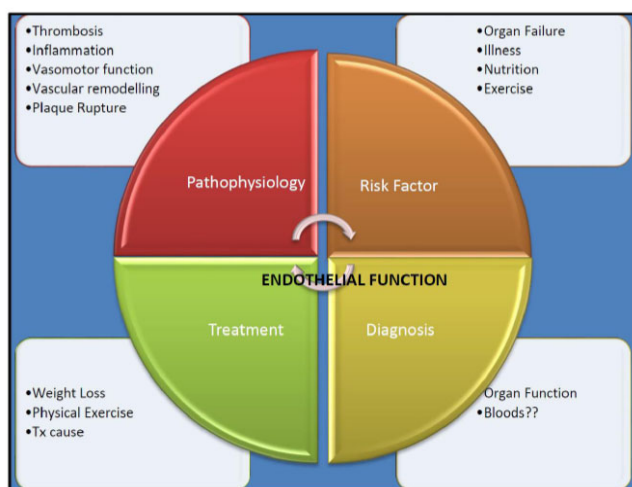
It is not feasible for a cardiologist to effect prognostic alterations in weight. On this particular condition, there are silos in medical practice as well as an allied health practice. Allied health services can only be attached to GP practices and care plans. Cardiologists can successfully address all the

major CV comorbidities; however, without an actual reduction in weight, the cost-efficiency of treatment becomes unclear [10, 12, 16].

### 2.3. Future Considerations

Health care funding and models for this comorbidity will remain challenging. Primary prevention has not been factored adequately and which metabolic disease actually manifests subsequently is unpredictable. There are duplications and inefficiencies in health encounters. Areas to consider:

- Charts to subcategorise obesity risk in individuals
- Charts to subcategorise obesity risk in established severe CHF
- Understanding body fat distribution, composition, and anthropometric index BMI
- Specialist health care plans
- Pathways of care/ services within health clusters for obesity with BMI >35 -40 kg/m<sup>2</sup>
- Greater access to public infrastructure, e.g., Rehab across the spectrum of care pre-emptively (primary) and improved secondary prevention
- White papers, e.g., identifying key common denominators (Fig. 1); Bariatric surgery



**Fig. (1).** Common denominator of endothelial function and cardiovascular diseases. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### 3. DIABETES AND HEART FAILURE

#### 3.1. Clinical Summary

Type 2 diabetes is a common comorbidity with heart failure. Between 25-45% of all patients admitted with acute heart failure have diabetes [1, 2]. Equally, patients with type 2 diabetes have an incidence of heart failure than those without diabetes [3]. The greater severity and complexity of the cardiac disease, as well as the underutilisation and relative resistance to conventional treatments, increases the risk for hospitalisation for heart failure [4], as well as readmission [5]. Ultimately, the prognosis and survival of patients with heart failure and diabetes have been approximately half observed in non-diabetic individuals, even after adjusting for conventional risk factors [6-8].

#### 3.2. What do Cardiologists Need to Know?

##### 3.2.1. It is not all about Atherosclerotic CVD

The management of cardiac risk in type 2 diabetes has traditionally focused on atherosclerotic MACE, prioritising lipid-lowering, antiplatelet therapies, and revascularization.

Although myocardial ischemia may be an important contributor to heart failure and its prognosis, many patients also have cardiac dysfunction due to microvascular disease, LVH, myocardial fibrosis, and functional changes in the diabetic myocardium (collectively known as *diabetic cardiomyopathy*). Ultimately, most deaths in this setting are sudden and related to decompensation rather than a new ischemic event. The pathophysiology remains inadequately treated in diabetic patients.

##### 3.2.2. Beta-Blockade can be Safe and Efficacious in Diabetes

Although  $\beta$ -blockers are widely used in patients with HFrEF, those with diabetes are less likely to receive  $\beta$ -blockers or have them up-titrated as recommended, even though trial data demonstrate improvements in morbidity, rate of hospitalisation, and mortality in this setting [9, 17]. This may partly reflect concerns for adverse effects on glucose and lipid control, hypoglycaemia, weight, hyperkalaemia, depression, fatigue, sleep and/or sexual function. However, newer “vasodilating  $\beta$ -blockers” may have superior tolerability in patients with diabetes when compared to traditional  $\beta$ -blockers [18].

##### 3.2.3. Mineralocorticoid Receptor Antagonists

Mineralocorticoid Receptor Antagonist (MRA) therapy is effective in diabetic patients with HFrEF. In addition, in symptomatic patients with HFpEF, MRA therapy can improve outcomes. However, hypokalemia and volume depletion are much more common in patients with diabetes, and MRAs must be used and dosed cautiously, and potassium levels closely monitored in this setting, even with newer MRAs like eplerenone and finerenone.

##### 3.2.4. New Combinations of Angiotensin Receptor Inhibitor and Nephilysin Inhibitor (ARNi)

ARNi is increasingly used in patients with HFrEF who continue to be symptomatic despite treatment with RAAS blockade and aldosterone antagonists. The overall response to and tolerability of ARNi in the subgroup of diabetic patients included in these trials were reassuringly similar or better for some parameters than in non-diabetic individuals [19], and the actions of neprilysin on cardiac fibrogenesis and remodelling make it a logical target for patients with diabetes and HFrEF. The ongoing PARAGON-HP will assess the broader utility of ARNi in patients with HFpEF, including 43% with diabetes.

##### 3.2.5. Atrial Fibrillation

Diabetes is recognised as an adverse prognostic feature in patients with atrial fibrillation, including those with heart failure.  $\beta$ -blockers are helpful for ventricular rate control, while non-dihydropyridine calcium entry blockers can also be helpful in patients with HFpEF. Catheter ablation for AF can be safe and effective in diabetic patients with HFrEF, who present with recurrent symptomatic AF, to decrease the rate of mortality and hospitalisation [20]. However, recur-

rence rates are higher in diabetic patients, and greater long-term follow-up complications are potentially offsetting the potential benefits of this catheter ablation.

### 3.2.6. Re-Admission can be Prevented

The majority of diabetic patients were admitted and then discharged with a primary diagnosis of heart failure. Most readmissions are not due to heart failure but rather due to co-morbidity, including arrhythmia, infection, Adverse Drug Reactions (ADRs), and renal impairment/reduced hydration [5, 21]. These many different reasons for readmission underline the critical value of multidisciplinary comprehensive care in all diabetic patients admitted with heart failure.

### 3.2.7. Choice of Glycaemic Control Agents can Affect Heart Failure

Poor glycaemic control in patients with diabetes is associated with an increased risk of heart failure and a poor prognosis [22]. However, glucose-lowering *per se* does not reduce new-onset heart failure or hospitalisation in patients with heart disease [23], while it carries risks including hypoglycaemia, weight gain, additional pill burden, and costs, leading to substantial therapeutic inertia towards improving glucose control in this setting. Nonetheless, careful optimisation of glycaemic control can reduce the risk of readmission following discharge, especially in those with poor glycaemic control (HbA1c  $\geq$  8% [64 mmol/mol]) [24]. Prioritising strategies that do not increase hypoglycaemia or fluid retention is also advantageous. In addition, the recent ADA/EASD consensus statement and ESC guidelines support the use of Sodium-Glucose co-transporter 2 (SGLT2) inhibitors, which have been reported to reduce HF admission in patients with diabetes and CVD [25] in a real-world setting [26].

### 3.3. Future Directions

Although the prognosis has substantially improved over the last 30 years [27], the increasing prevalence of CVD diabetes means that more and more patients with diabetes will require treatment for heart failure, both in primary care and hospital. The majority of these individuals will have HFpEF, for which there is currently limited data for interventions. Future studies, including those with SGLT2 inhibitors and ARNi, are planned to address this gap. However, treatments at an earlier asymptomatic stage (detected as diastolic dysfunction or reduced contractile reserve) remain to be validated. Future interventions specifically targeting key pathogenic pathways, including altered calcium homeostasis, cardiac metabolism, inflammation, and fibrogenesis, are still needed.

## 4. OLDER PATIENTS AND MEDICATION CONSIDERATIONS

### 4.1. Clinical Summary

Older adults over 60 years old are at a leading risk for most Cardiovascular Diseases (CVD) due to a combination

of accumulating modifiable risk and aging processes [25]. CHF is predominately a syndrome seen with increasing aging that has a cause and aggravates risk factors, comorbid conditions, including psychological and social vulnerability, as well as geriatric syndromes such as falls, confusion, and frailty. All MACE are worse with advancing ages, including rehospitalisation, which is a lead cause for patients > 65 years of age. It can also be classified as an epidemic in the elderly, currently utilising >2% of health budgets predominately related to readmission and rates projected to increase over the next several decades [27, 28].

### 4.2. What Cardiologist's Need to Know

Echocardiography classifies CHF equally as predominately HFrEF and HFpEF. The clinical profile in the latter differs, being more prevalent in women (>60%), older, more obese, and contributing differently to risk. Current trends project HFpEF to be the most prevalent form of CHF within one decade; the current prevalence is 1-5.5%, increasing 1% yearly [29, 30]. Post-discharge >30% will be hospitalised or die [31]. The elderly are challenged with additional factors; some establish the prevalence of cognitive decline or mood disorders or depression and decompensated HF presenting as pseudodementia; and other novel areas include peripheral changes in the musculoskeletal system, vascular system, and systemic changes in metabolism [32-34]. Three important factors require specific consideration: firstly, altered physiology of aging, altered pharmacodynamics, particularly with hepatic and renal impairment, and pharmacokinetics with reduced total body water content, body mass, and fat tissue. The ensuing reduction in the volume of distribution influences plasma concentrations of lipophilic or hydrophilic drugs; secondly, the combination of comorbidity (two thirds > 2 and one in four have 6 or more noncardiac comorbidities) influences compliance and lowers safety for adverse events; thirdly, social isolation and poor self-efficacy alters MACE.

### 4.3. Future Considerations

CHF in the elderly is complex, and a surgical approach is needed. As readmission, the leading factor in health cost is linked to morbidity and mortality outcomes, and a concerted focus must be placed on this performance indicator.

- Epidemiology - prospective CHF databases collecting information across a patient's health care journey will allow a better understanding of the differences in both forms of CHF and will be best to target strategies.
- Readmissions: ensuring process of care similar to the OPTIMIZE-HF study are in place; with a shared understanding from stakeholders in the health cluster.
- Treatment considerations [35]: ensuring that a complex care team is involved in difficult management decisions especially when drugs need to be omitted. Novel targets are being explored predominately for DHF, which should be mentioned in guidelines. Optimising medication safety, exploring pill burden, and

optimal device utility will require increase local expertise and training. Some points will be difficult to place into guidelines, but generic pillars will develop to guide case by case decision making.

### 5. FUTURE DIRECTIONS

The greatest impacts on CHF outcomes from trials were from therapeutics delivered within a RCT machinery and post-trial structured service based around the OPTIMIZE-HF design. The discovery of novel pharmaceuticals appears to have plateaued; however, achieving improved outcomes from the available agents requires more impetus, as the goals are realistic and achievable. As an example, within the Australian Medicare-funded health system, funding to provide therapies generated from RCT is just to ensure that the delivery mechanisms for communities are in place. It is thus impossible to guarantee trial evidence is replicated across the health spectrum. Phase 4 research must play a greater role in health clusters (Fig. 2). It is due to these points we should explore future needs starting with a curriculum for specialist trainees in these areas:

#### 5.1. Terminology

Several important terms should become common ‘lingo’ among practising clinicians and implemented into the quality assurance of practices (Fig. 3):

- Disease Management - is a systematic process with six arms involving identification of the population, utilization of evidence-based practise, a collaborative practice model (e.g., including physicians to support service providers), support by patient self-management and finally in doing so factor in education, processes and outcomes measurement or evaluation in a feedback loop with routine reporting. In a CHF chronic care model, various participants provide ‘disease management support’ such as case management, gatekeeping and/or multidisciplinary care.
- Taxonomy [21] - a system of classification, e.g., International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) or Disease Management (Fig. 1) [21].
- Process of care [21-23] - defines a cluster of terms that incorporates and overlaps ‘performance’ or ‘quality of care’ measurements. It involves standardizing (defining), collecting, analysing, and reporting of information; define ‘Terms of reference’ (e.g., a subject or entity) providing health services. It is the most valuable measure of cost-efficacy to patients and stakeholders. Key performance indicators involve a methodology to determine the most critical performance measures. The parameters are based on scientific evidence that reflects guidelines, practice parameters, and standards of care. Findings are provided objectively as a numerical or percentage; however, subjective elements must increasingly be considered.



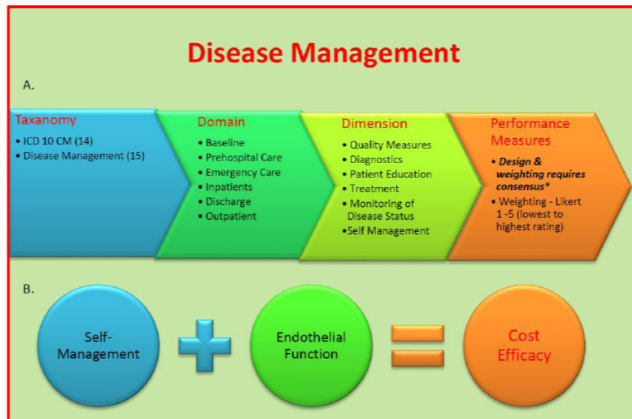
**Fig. (2).** Model of training and practice and potential missing links; **A.** Governments provide accreditation bodies the authority to determine the scope and breadth of training for cardiologists servicing health clusters. Regulatory authorities supervise this process. Clinical services are then provided, and standards are required, again supervised by accrediting bodies and monitored by regulatory bodies. The issue for the present is the communication of these two bodies to shape the needs of an individual health cluster. For e.g., a cardiology practice in remote Aboriginal communities will differ from one in a low socioeconomic, multiethnic community. **B.** Essential elements for training and practice are highlighted. At each stage, greater emphasis is placed on different elements. For optimal cost-efficiency, all these elements should be present; however, it is not always possible in clinical practice. Leveraging/ facilitating cooperation across the spectrum of that speciality can ensure trainee specialist communication/ corporation facilitates continuity of standards on either side. A ‘Community Consultant’ could be the missing link in the current system to feedback specific issues to relevant authorities. It is hoped this type of position could provide training modules to specialists, a guide to existing workforce reskilling, and match trainee interest to additional curriculum modules with the needs of a health cluster. Cardiology training in Australia is regulated by the Royal Australasian College of Physicians (RACP). Upon completion, a fellowship is obtained that allows accreditation via the Australian Health Practitioner Regulation Agency (AH-PRA). These organisations then require standards that need to be maintained through self-reporting of continuous medical education. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

- Cost-effectiveness [25] - economic analysis comparing the relative costs and effects (outcomes) of an aspect disease management expressed as a ratio with numerator as a cost associated with health gain and denominator gains in health (e.g., years of life, deaths averted).

Pathways for clinical practice and Medicare Gaps - it is becoming increasingly difficult to practice in isolation and leverage hospital infrastructure and meet cost-efficiency



standards. The Medicare locals, GP Superclinics, and Chronic Diseases Team Care Plans billing items aimed to address this, were not as successful as anticipated. Outpatient services are best to run in the community close to patients, and it may never be favourable for public hospitals to compete for this except for advanced subspecialty services. Future plans must incorporate greater avenues for both specialist and general practitioners to uniformly access these services in the care plans. Greater oversight must be provided for documented team meetings between the parties in the plan to achieve targets and have access to all required services [17].



**Fig. (3).** Disease Management components, Measuring Performance and Cost Efficacy; **(A)** Disease management is now standardised through well-established taxonomies. Designing a model of care requires an understanding of historical and current modelling of future care. Within each health cluster, disease management programs are designed that administer care *via* domains. Dimensions of care are specific aspects of care within each domain. In defining the key performance indicators from established performance measures, collaboration is required between stakeholders. Bodies such as the Royal Australasian College of Physicians (RACP) could play important roles in a given endorsement or validating the ‘Process of Care’ findings. This will ensure a step lock measure in the process and enhance credibility for translational works or even go further to define the priority areas research bodies could fund. **(B)** Finally, cost-efficacy includes both clinical and research works. As there are significant overlaps for high value works across cardiac and comorbidity associated specialties, collaboration across a broader alliance could provide data to identify the loci for cost efficacy disease management targets. (*A higher resolution / colour version of this figure is available in the electronic copy of the article.*)

- Subspecialist Education Curriculum - two areas could be considered. During training, greater emphasis on models of care including self-care, audits, and importance of cost-efficacy in clinical practice; second in practice, assistance in achieving continuous medical education in areas relevant to patients and care required in the practising health cluster. Where there are gaps in facilitations for research institutes, consultancy should be initially offered, or an audit should be conducted if needed. The results of which

should trackback to the funding administration of that cluster. Self-management deserves special mention as large sums of money have been invested; however, translational issues still remain. It remains the most cost-efficacious common denominator to reduce all MACE. We reference some of our earlier publications for readers [18-20]. A proposed schema for future works is enclosed (Fig. 2). While scores capture the risk of one disease, they do not factor risk for associated comorbidities, *e.g.*, at least 50% of CHF readmission are non-cardiac [1]. Thus nesting comorbidities sub-studies in larger CHF research, including epidemiology, *e.g.*, performance measures to basic sciences, is important but requires a coordinated approach.

- Prospective Registries - information on deaths are readily accessible. Real-time databases are limited to medical procedures and are selective. With the advent of data mining technologies, the standardisation of digital data into systems require greater exploration. Large registries across health clusters rarely have the power to define local solutions. Nested health cluster registries within a state or national registry must be given priority if we have to improve health care with increased levels of complexity [21-26]. Several priority areas of overlap include clinical self-management efficacy Table 2 and basic science advancement of endothelial function (Fig. 3) translational works.

In Table 2, we propose a framework for a clinical tool to assess Congestive Heart Failure (CHF) and readmission risk for ambulatory patients, by defining the actionable care areas to distribute resources following first and early encounters. The need for such a tool is evident following outpatients and new emergency department presentations. Among some successfully translated clinical tools in cardiovascular medicines are CHADVASC-2 and HASBLED scoring system for Atrial Fibrillation (AF). A translatable tool for CHF has been less forthcoming. Fundamental differences in disease processes exist between CHF and AF; firstly in defining the risk, in this case, readmission as opposed to stroke; secondly, the domains and dimensions of care influence this risk mostly; and finally, the scoring system to execute the management strategy, with CHF a basket of options unlike fixed haematological strategies with AF. A CHF scoring system has thus more interactive components, but the ease of use is more or less similar as with the AF scores. We have thus isolated the clinical assessment needs to: 1) specific high-risk readmission criteria: including comorbidities, mood, the current quality of life, social circumstances, and compliance, 2) ability to manage independently - grades of self-care ability and efficacy, 3) additional support domains required and 4) final score and health services support to be mobilised. We cite references for previously published work on each of the areas, individually [1-9, 17, 18, 20, 24, 25]. A combined approach is the current focus. (See Appendix 1).

### 5.2. Health Clusters and Common Goals

The needs of health systems are not homogenous. The medicare program, however, has narrow funding goals. Defining health clusters in each Australian state will allow jurisdiction and accountability. It also provides an opportunity to define the constituents (patient population) and their needs, as well as stakeholders who should be participants in

the goals set in that cluster. This should rightfully include a spectrum from primary care, tertiary and quaternary care, allied health, and government administrators.

### 5.3. Advocacy & White Papers

Among the greatest impacts of an organisation is that any positions taken represent a consensus of sorts. The advocacy arm of medical bodies must devote a proportion of

**Table 2. Heart failure ambulatory readmission risk scoring tool.**

Domains of Care	Heart Failure Ambulatory Readmission Risk Dimensions of Care	#Yes	No	*D
<b>1. Baseline readmission risk</b>	1. Comorbid risk	1-3+	0	-
	2. Managing ADL	1	0	-
	3. Adequate Social supports	1	0	-
	4. Compliance	1	0	-
	5. Mood - neurovegetative, psychological (Ref 4)	1	0	-
<b>2. Living at home (Skills &amp; Goals)</b> a. Self-care Maintenance b. Self-care Management c. Self-Care Confidence/Efficacy	<b>a. Do you know “how to (skill)..to achieve (goal)”...</b>			
	6. Problem Solve - e.g i) monitoring;	0 or -1	1	-
	7. Decision making question	0 or -1	1	-
	8. About physical function - e.g i) exercise	0 or -1	1	-
	<b>b. Do you know “what to do if (skill) to achieve (goal)”...</b>			
	9. Resource utilization e.g i) monitoring with action	0 or -1	1	-
	10. Form patient-provider partnership e.g i) engage health system	0 or -1	1	-
	11. Action planning when self-tailoring	0 or -1	1	-
	<b>c. Do you know “how confident you are (skill)...when faced with (goal)”</b>			
	12. Has the client previously received rehab/education? State-level of Self-Care Confidence (SR, SE, TI, TE) - e.g. i) adherence to diet ii) compliance	0 or -1	1	-
	<b>3. Supports for living at home</b>	13. Do you need additional services	0 or -1	1
<b>4. Chronology</b>	14. Presentation of CHF or comorbidity acute (1) or subacute-chronic (0). (If acute, go to long-form; cood with inpt team).	1	0	-
<b>5. TOTAL SCORE</b> (NB// minus score given if excellent self-care capacity or support)		-		-
<b>6. HF Team (HFT)</b>	15. Correspondence to (dn, gp, ot, n, p, ph, r, shf, so, others)	-		-
<b>Service Delivery Needs</b>				
<b>Score ≤ 1 in each dimension or requires &lt; 1 domain of care</b>	<b>Score = 2 in at least 2 or more for any dimension or &gt;1 domain of care</b>	<b>Score ≥ 3 for any dimension or &gt; 2 for a dimension or domain of care</b>		
A patient has low re-admission risk and can self- manage. Reassess bi-annually	A patient has moderate readmission risk and may have limited self-care capability	The patient is likely to be at a high risk of readmission and probably does not have the capacity to self-care independently		
Short-term allied health support and self-care education may be appropriate. Patient may be a good candidate for technology-assisted out-patient HF programs	Medium to long-term allied health support and self-care education may be appropriate. Patient may be a candidate for technology-assisted out-patient HF programs	Long-term allied health support and nurse-led out-patient support are likely to be needed. Patient is unlikely to independently self-care.		
<b>Tailored Resources Required</b>				
<b>Domain combinations (C; H; T)</b>	<b>Dimension hierarchy (R; S; A)</b>	<b>Duration: (S; M; L)</b>	<b>Notes:</b> -Intervention Model (I) -Other consideration	



resources addressing pressing issues. These can be national or regional. The mechanism by which such matters are raised is unclear. One method would be a call for submission over a two-year term. These issues are then raised and voted on. The issues receiving support will be supported through a 'White Paper'.

## CONCLUSION

Comorbidities associated with CHF are associated with greater MACE, cost, and complexity of care. Current and future guidelines are unlikely to provide greater clarity for management. Quality improvement studies such as OPTIMIZE-HF have shown that administering guideline care achieves desired outcomes. In Australia, there are many confounders that hinder achieving this goal. While it is essential to focus on CHF and each comorbidity, it is also vital to focus on care models. Defining this within a health cluster is likely to provide the greatest benefits. We have highlighted several key comorbidities, outlined broad approaches for them, and explored a care model that provides opportunities and solutions for trainees and physicians in a collaborative approach. We would encourage more robust discussions in this area to bring attention and facilitate long term solutions in the medicare funded model of care. Two areas of common overlap between CHF and any associated comorbidity are self-management and endothelial dysfunction. Larger studies involving any of these syndromes should consider nesting other comorbidities as sub-studies.

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## APPENDIX 1 ABBREVIATIONS FOR TABLE

**ABBREVIATIONS:** (Infrastructure - use large caps; Personnel - use lower caps)

**Self-Care SKILLS:** 1) Problem solving, 2) Decision making, 3) Resource utilization, 4) Form patient-provider partnership, 5) Action planning with Self-tailoring.

**Self-Care GOALS** 1) Monitoring (G,M), 2) Monitoring with action (G), 3) Exercise (G,M), 4) RF Modification and preventive behaviours (G), 5) Engaging health system (G,M), 6) Compliance (G,M,P), 7) Diet adherence (G,M,P).

\***D** = domain of care to action deficit. A/C = Ambulatory or Community; H = hospital; T = technology assisted CHF care; I = intervention category (potential overlap); HFT = heart failure team.

• C1 - GP; C2 - cardiologist; C3 - community allied health.

• H1 - ED; H2 - specialist clinics; H3 - hospital allied health.

• T1 - phone; T2 - mobile; T3 - internet.

• I1 - Case management; I2 - Chronic care model; I3 - discharge management; I4 - Multidisciplinary team; I5 - Complex intervention; I6 - primary or secondary care follow-up; I7- self-care.

• HFT - h = hospital; p = private; dn - district nurse; gp - general practitioners; n - nurse; ot - occupational therapist; p - physiotherapy; ph - pharmacy; ps - psychologist; r - rehab; shf = HF specialist; so - other specialist.

• #**Yes** = dimensions of care to action within each health care domain. R = highest readmission risks; S = self-care; A = ambulatory care at home.

• R1 - Comorbidity; R2 - Functioning (physical, occupational, perceptions on health (potential overlap), personal belief (potential overlap), psychological and social functioning (potential overlap); R3 - social supports; R4 - mood (neurovegetative, psychological); R5 - compliance.

S1 - Patient Activation (items 1-3); S2 Delivery System Design/Decision Support (items 4-6); S3 - Goal Setting (items 7-11); S4 - Problem-solving/Contextual Counselling (items 12-15); S5 - Follow-up/Coordination (items 16-20). (SR - symptom recognition; SE - symptom evaluation; TI - treatment implementation; TE - treatment evaluation).

• A1 - independent; A2 - some supports; A3 - dependant.

**Duration:** S - Short; M - Medium; L - Long-term.

## REFERENCES

- [1] Iyngkaran P, Liew D, Neil C, Driscoll A, Marwick TH, Hare DL. Moving from heart failure guidelines to clinical practice: gaps contributing to readmissions in patients with multiple comorbidities and older age. *Clin Med Insights Cardiol* 2018; 12: 1179546818809358. <http://dx.doi.org/10.1177/1179546818809358> PMID: 30618487
- [2] Fonarow GC, Albert NM, Curtis AB, *et al.* Associations between outpatient heart failure process-of-care measures and mortality. *Circulation* 2011; 123(15): 1601-10. <http://dx.doi.org/10.1161/CIRCULATIONAHA.110.989632> PMID: 21464053
- [3] Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2018; 5(4): 685-94. <http://dx.doi.org/10.1002/ehf2.12283> PMID: 29660263
- [4] Iyngkaran P, Majoni W, Cass A, *et al.* Northern Territory perspectives on heart failure with comorbidities – understanding trial validity and exploring collaborative opportunities to broaden the evidence base. *Heart Lung Circ* 2015; 24(6): 536-43. <http://dx.doi.org/10.1016/j.hlc.2014.12.007> PMID: 25637942
- [5] Iyngkaran P, Harris M, Ilton M, *et al.* Implementing guideline based heart failure care in the Northern Territory: challenges and solutions. *Heart Lung Circ* 2014; 23(5): 391-406. <http://dx.doi.org/10.1016/j.hlc.2013.12.005> PMID: 24548637
- [6] Iyngkaran P, Thomas M, Majoni W, Anavekar NS, Ronco C. Comorbid heart failure and renal impairment: epidemiology and management. *Cardiorenal Med* 2012; 2(4): 281-97.

- [7] <http://dx.doi.org/10.1159/000342487> PMID: 23381594  
Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardio-renal syndrome. *J Am Coll Cardiol* 2008; 52(19): 1527-39.  
<http://dx.doi.org/10.1016/j.jacc.2008.07.051> PMID: 19007588
- [8] Iyngkaran P, Schneider H, Devarajan P, Anavekar N, Krum H, Ronco C. Cardio-renal syndrome: new perspective in diagnostics. *Semin Nephrol* 2012; 32(1): 3-17.  
<http://dx.doi.org/10.1016/j.semnephrol.2011.11.002> PMID: 22365157
- [9] Matsushita K, Minamishima T, Sakata K, Satoh T, Yoshino H. Prognostic factors for one-year mortality in patients with acute heart failure with and without chronic kidney disease: differential impact of beta-blocker and diuretic treatments. *Hypertens Res* 2019; 42(7): 1011-8.  
<http://dx.doi.org/10.1038/s41440-018-0204-4> PMID: 30659283
- [10] The relationship between overweight, obesity and cardiovascular disease: a literature review prepared for the National Heart Foundation Australia. Canberra: AIHW 2004.
- [11] Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; 444(7121): 881-7.  
<http://dx.doi.org/10.1038/nature05488> PMID: 17167477
- [12] Kim SH, Després JP, Koh KK. Obesity and cardiovascular disease: friend or foe? *Eur Heart J* 2016; 37(48): 3560-8.  
<http://dx.doi.org/10.1093/eurheartj/ehv509> PMID: 26685971
- [13] Lavie CJ, De Schutter A, Milani RV. Healthy obese versus unhealthy lean: the obesity paradox. *Nat Rev Endocrinol* 2015; 11(1): 55-62.  
<http://dx.doi.org/10.1038/nrendo.2014.165> PMID: 25265977
- [14] Chrysant SG, Chrysant GS. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. *J Am Soc Hypertens* 2013; 7(1): 85-94.  
<http://dx.doi.org/10.1016/j.jash.2012.11.008> PMID: 23321407
- [15] Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008; 156(1): 13-22.  
<http://dx.doi.org/10.1016/j.ahj.2008.02.014> PMID: 18585492
- [16] Csige I, Ujvárosy D, Szabó Z, et al. The impact of obesity on the cardiovascular system. *J Diabetes Res* 2018; 2018: 3407306.  
<http://dx.doi.org/10.1155/2018/3407306> PMID: 30525052
- [17] Penn M, Bhatnagar S, Kuy S, et al. Comparison of wait times for new patients between the private sector and united states department of veterans affairs medical centers. *JAMA Netw Open* 2019; 2(1): e187096.  
<http://dx.doi.org/10.1001/jamanetworkopen.2018.7096> PMID: 30657532
- [18] Iyngkaran P, Toukhsati SR, Harris M, et al. Self managing heart failure in remote Australia - translating concepts into clinical practice. *Curr Cardiol Rev* 2016; 12(4): 270-84.  
<http://dx.doi.org/10.2174/1573403X12666160703183001> PMID: 27397492
- [19] Sharma A, Zhao X, Hammill BG, et al. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the get with the Guidelines-Heart Failure Registry. *Circ Heart Fail* 2018; 11(6): e004646.  
<http://dx.doi.org/10.1161/CIRCHEARTFAILURE.117.004646> PMID: 29793934
- [20] Iyngkaran P, Majoni V, Nadarajan K, et al. AUSTRALIAN Indigenous Chronic Disease Optimisation Study (AUSI-CDS) prospective observational cohort study to determine if an established chronic disease health care model can be used to deliver better heart failure care among remote Indigenous Australians: Proof of concept-study rationale and protocol. *Heart Lung Circ* 2013; 22(11): 930-9.  
<http://dx.doi.org/10.1016/j.hlc.2013.04.001> PMID: 23689164
- [21] Krumholz HM, Currie PM, Riegel B, et al. A taxonomy for disease management: a scientific statement from the American Heart Association Disease Management Taxonomy Writing Group. *Circulation* 2006; 114(13): 1432-45.  
<http://dx.doi.org/10.1161/CIRCULATIONAHA.106.177322> PMID: 16952985
- [22] Bonow RO, Bennett S, Casey DE, et al. Clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures. *Circulation* 2005; 112: 1853-87.  
<http://dx.doi.org/10.1161/CIRCULATIONAHA.105.170072> PMID: 16160201
- [23] Spertus JA, Bonow RO, Chan P, et al. ACCF/AHA new insights into the methodology of performance measurement: a report of the American College of Cardiology Foundation/American Heart Association Task Force on performance measures. *Circulation* 2010; 122(20): 2091-106.  
<http://dx.doi.org/10.1161/CIR.0b013e3181f7d78c> PMID: 21060078
- [24] Iyngkaran P, Tinsley J, Smith D, et al. Northern Territory Heart Failure Initiative-Clinical Audit (NTHFI-CA)-a prospective database on the quality of care and outcomes for acute decompensated heart failure admission in the Northern Territory: study design and rationale. *BMJ Open* 2014; 4(1): e004137. [Erratum in: *BMJ Open*. 2014; 4(2): e004137corr1].  
<http://dx.doi.org/10.1136/bmjopen-2013-004137> PMID: 24477314
- [25] Iyngkaran P, Liew D, McDonald P, et al. Phase 4 studies in heart failure - what is done and what is needed? *Curr Cardiol Rev* 2016; 12(3): 216-30.  
<http://dx.doi.org/10.2174/1573403X12666160606121458> PMID: 27280303
- [26] Nanayakkara S, Marwick TH, Kaye DM. The ageing heart: the systemic and coronary circulation. *Heart* 2018; 104(5): 370-6.  
<http://dx.doi.org/10.1136/heartjnl-2017-312114> PMID: 29092917
- [27] Nanayakkara S, Patel HC, Kaye DM. Hospitalisation in patients with heart failure with preserved ejection fraction. *Clin Med Insights Cardiol* 2018; 12: 1179546817751609.  
<http://dx.doi.org/10.1177/1179546817751609> PMID: 29343997
- [28] Nanayakkara S, Kaye DM. Management of heart failure with preserved ejection fraction: a review. *Clin Ther* 2015; 37(10): 2186-98.  
<http://dx.doi.org/10.1016/j.clinthera.2015.08.005> PMID: 26385583
- [29] Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; 126(1): 65-75.  
<http://dx.doi.org/10.1161/CIRCULATIONAHA.111.080770> PMID: 22615345
- [30] Braunwald E. Heart failure. *JACC Heart Fail* 2013; 1(1): 1-20.  
<http://dx.doi.org/10.1016/j.jchf.2012.10.002> PMID: 24621794
- [31] Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007; 50(8): 768-77.  
<http://dx.doi.org/10.1016/j.jacc.2007.04.064> PMID: 17707182
- [32] Upadhyaya B, Taffet GE, Cheng CP, Kitzman DW. Heart failure with preserved ejection fraction in the elderly: scope of the problem. *J Mol Cell Cardiol* 2015; 83: 73-87.  
<http://dx.doi.org/10.1016/j.yjmcc.2015.02.025> PMID: 25754674
- [33] Xanthopoulos A, Triposkiadis F, Starling RC. Heart failure with preserved ejection fraction: Classification based upon phenotype is essential for diagnosis and treatment. *Trends Cardiovasc Med* 2018; 28(6): 392-400.  
<http://dx.doi.org/10.1016/j.tcm.2018.01.001> PMID: 29471985
- [34] Nanayakkara S, Haykowsky M, Mariani J, et al. Hemodynamic profile of patients with heart failure and preserved ejection fraction vary by age. *J Am Heart Assoc* 2017; 6(9): e005434.  
<http://dx.doi.org/10.1161/JAHA.116.005434> PMID: 28939710
- [35] Nanayakkara S, Kaye DM. Targets for heart failure with preserved ejection fraction. *Clin Pharmacol Ther* 2017; 102(2): 228-37.  
<http://dx.doi.org/10.1002/cpt.723> PMID: 28466986