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Guideline-Led Prescribing to Heart Failure Patients in Ireland and Egypt

Seif Yahia Salah El Hadidi (BSc. Pharm)

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Pharmacy

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Head of School

Professor Stephen Byrne

Supervisors

Doctor Margaret Bermingham

Professor Stephen Byrne

Professor Ebtissam Darweesh

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List of Abbreviations

ACE	angiotensin-converting enzyme
ADHERE	Acute Decompensated Heart failure national REgistry
A-HeFT	African American Heart Failure Trial
ARB	angiotensin-II receptor blocker
ARNi	angiotensin receptor-neprilysin inhibitor
ATLAS	Assessment of Treatment with Lisinopril And Survival clinical trial
AV-block	atrioventricular block
BIOSTAT-CHF	BIOlogy Study to TAilored Treatment in Chronic Heart Failure registry
BP	blood pressure
bpm	beats per minute
CCB	calcium channel blocker
CCU	Critical Care Unit
CHAMP-HF	Change the Management of Patients with Heart Failure registry
CHARM-PRESERVED	Candesartan cilextil in Heart failure Assessment of Reduction in Mortality clinical trial
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CKD	chronic kidney disease
CPD	continuous professional development
CRT	cardiac resynchronisation therapy
CVA	cerebrovascular accident
DMP	disease-management programme

DREAM	Diabetes REduction Assessment with ramipril and rosiglitazone Medication clinical trial
€	Euro
EBBB	evidence-based beta-blocker
EF	Ejection Fraction
EHFS II	European Heart Failure Survey II
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure clinical trial
ESC	European Society of Cardiology
ESC-HF	European Society of Cardiology – Heart Failure Long-Term Registry
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan clinical trial
GAI	Guideline Adherence Index
GOLD-HF	Geriatric Outcomes and Longitudinal Decline in Heart Failure study
GP	General Practitioner
GRACE	Good ReseArch for Comparative Effectiveness
H-ISDN	hydralazine-isosorbide dinitrate
HEAAL	Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure clinical trial
HF	Heart Failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
ICD	implantable cardiac defibrillator

INTER-CHF	international congestive heart failure registry
I-PREFER	Identification of patients with heart failure and PREserved systolic Function
IQR	interquartile range
IRER	Individualized Recommended Evidence-based Reconciliation
IT	information technology
K	serum potassium
LCL	lower confidence level
L-MICs	low-middle income countries
LTC	Long-Term Care
LVAD	Left Ventricular Assist Device
MAP	mean arterial blood pressure
MDRD	modified diet for renal disease
MENA	Middle East and North Africa
mg/day	milligram per day
mGAI	modified Guideline Adherence Index
ml/min.	millilitre per minute
mmHg	millimetre of mercury
MRA	mineralocorticoid receptor antagonist
MUH	Mercy University Hospital
N/A	not available
N	number
NDP-CCB	non-dihydropyridine calcium channel blocker
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OPTIMIZE-HF	Organized Program To Initiate Lifesaving TreatMent in HospitalIZEd patients with Heart Failure registry

OR	odds ratio
PARADIGM-HF	Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure clinical trial
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure clinical trial
PIMHF	Potentially Inappropriate Medicines in Heart Failure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUALIFY	QUality of Adherence to guidelines' recommendations for LIFe-saving treatment in heart failure survey
RAAS	renin-angiotensin-aldosterone system
RAASi	renin-angiotensin-aldosterone system inhibitor
RALES	Randomized Aldactone Evaluation Study clinical trial
RASi	renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker)
RCT	randomised clinical trial
REALITY-AHF	Registry Focused on Very Early Presentation and Treatment in the Emergency Department of Acute Heart Failure
REC-FPSPI	Research and Ethics Committee of Faculty of Pharmaceutical Sciences and Pharmaceutical Industries
SD	Standard Deviation
SHIFT	Systolic Heart failure treatment with the I*f* inhibitor ivabradine clinical trial
SPSS	IBM Statistical Package for the Social Sciences
SR – MA	systematic review and meta-analysis
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions

STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TD	target dose
THESUS-HF	The Sub-Saharan Africa Survey of Heart Failure registry
TIME-CHF	Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure
TOPCAT	Treatment Of Preserved Cardiac function in heart failure with an Aldosterone antagonist clinical trial
UCL	upper confidence level
UK	United Kingdom
USA	United States of America
US$	United States Dollar

Declaration

I declare that this thesis has not been submitted for another degree either at University College Cork or elsewhere. The work, upon which the thesis is based, was carried out in collaboration with a team of supervisors who are duly acknowledged in the text of the thesis. Apart from due acknowledgement, it is entirely my own work. The Library may lend or copy this thesis upon request.

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Publications and presentations

Published research papers

A tool for assessment of heart failure prescribing quality: a systematic review and meta-analysis.

El Hadidi S, Darweesh E, Byrne S, Bermingham M. Pharmacoepidemiol Drug Saf. 2018 Jul;27(7):685-694

Research papers under review

Guideline-led prescribing to heart failure patients at discharge from a critical care unit: the impact of a clinical pharmacy service.

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

Submitted to Scientific Reports Journal, August 2019.

Factors influencing guideline-led prescribing to heart failure patients: a novel questionnaire in a critical care setting

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

Submitted to International Journal of Clinical Pharmacy, July 2019.

Conference presentations

Oral Presentations

Guideline-led prescribing to heart failure patients at discharge from a critical care unit: the impact of a clinical pharmacy service

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

41st All Ireland Schools of Pharmacy Conference, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland, April 2019.

Impact of a clinical pharmacy service on heart failure guideline-led prescribing at discharge in an Egyptian critical care unit.

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

5th FUE International Conference of Pharmaceutical Sciences, Future University in Egypt, Cairo, Egypt. January 2019.

Potentially Inappropriate Medicines in Heart Failure Tool: application in an Irish Long-Term Care setting.

El Hadidi S, O'Sullivan D, O'Mahony D, Darweesh E, Byrne S, Bermingham M.

Irish Cardiac Society Annual Scientific Meeting. Derry, Northern Ireland, October 2017.

Published: *Heart. 2017;103 (Suppl 6): A1–A39:A1.-A DOI: 10.1136/heartjnl-2017-ICS17.1.*

Guideline-led prescribing among heart failure patients in the Long-Term Care setting.

El Hadidi S, O'Sullivan D, O'Mahony D, Darweesh E, Byrne S, Bermingham M.

39th All Ireland Schools of Pharmacy Conference, School of Pharmacy, University College Cork, Cork, Ireland, April 2017.

Appropriate prescribing in heart failure in Ireland and Egypt.

El Hadidi S, Byrne S, Darweesh E, Bermingham M.

38th All Ireland Schools of Pharmacy Conference, School of Pharmacy, Royal College of Surgeons in Ireland, Dublin, Ireland. March 2016.

Conference poster presentations

Impact of a clinical pharmacy service on heart failure guideline-led prescribing at discharge in an Egyptian critical care unit.

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

European Society of Cardiology Heart Failure Association Annual Congress 2019. Athens, Greece. May 2019.

Published: *European Journal of Heart Failure (2019) 21 (Suppl. S1) 5–592; DOI:10.1002/ejhf.1488*

Factors influencing guideline-led prescribing to heart failure patients in an Egyptian critical care setting

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

European Society of Cardiology Heart Failure Association Annual Congress 2019. Athens, Greece. May 2019.

Published: *European Journal of Heart Failure (2019) 21 (Suppl. S1) 5–592; DOI:10.1002/ejhf.1488*

Factors influencing guideline-led prescribing to heart failure patients in an Egyptian critical care setting

El Hadidi S, Bazan NS, Darweesh E, Byrne S, Bermingham M.

5th FUE International Conference of Pharmaceutical Sciences. Future University in Egypt, Cairo, Egypt. January 2019.

Identifying potentially inappropriate medicines use among heart failure patients in Long-Term Care using a disease-specific tool.

El Hadidi S, O'Sullivan D, O'Mahony D, Darweesh E, Byrne S, Bermingham M.

European Society of Cardiology Heart Failure Congress. Paris, May 2017.

Published: *European Journal of Heart Failure (2017) 19 (Suppl. S1):223.*

Guideline-led prescribing among heart failure patients in the Long-Term Care setting.

El Hadidi S, O'Sullivan D, O'Mahony D, Darweesh E, Byrne S, Bermingham M.

European Society of Cardiology Heart Failure Congress. Paris, May 2017.

Published: *European Journal of Heart Failure (2017) 19 (Suppl. S1):222.*

The Guideline Adherence Index as an objective evaluator of appropriate prescribing in heart failure: a meta-analysis.

El Hadidi S, Darweesh E, Byrne S, Bermingham M.

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Published: *International Journal of Pharmacy Practice, 25(Suppl 1); 58.*

The Guideline Adherence Index as an objective evaluator of appropriate prescribing in heart failure: a meta-analysis.

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Thesis Abstract

Introduction

Guidelines strongly recommend patients with Heart Failure (HF) be treated with multiple medications proven to improve clinical outcomes, as tolerated. Guideline-led prescribing of HF evidence-based medicines is strongly associated with improved survival, prognosis, and quality of life in HF. The guidelines strongly recommend, and the optimal patient outcomes are achieved with an appropriate prescription of target doses of all HF therapies. The degree to which gaps in medication use and dosing persist in contemporary Irish or Egyptian practices is unclear.

Aim

To assess guideline-led prescribing of the evidence-based HF medications in routine clinical practice in Ireland and Egypt and to assess the prevalence of HF-specific potentially inappropriate prescribing in the same Irish and Egyptian clinical settings.

Method

Firstly, a narrative literature review was undertaken to determine and compare the available data and gaps in knowledge regarding HF management in Ireland as a developed European country, and Egypt as a developing Middle-Eastern country, with a particular focus on the guideline-directed medical therapies. Secondly, a systematic review was undertaken to identify the objective quantitative tools to assess the quality of HF prescribing practice. Next, a prospective cohort study was conducted on an Irish outpatient population to evaluate the extent of use and dosing of the guideline-directed medical therapies. Then, a multicentre retrospective

study was carried out in 14 Long-Term Care (LTC) facilities in Cork County to assess the prevalence of appropriate and potentially inappropriate prescribing practices. In Egypt, a longitudinal observational study was conducted in order to evaluate the prescribing quality and patterns in HF patients in an Egyptian critical care setting at discharge. Finally, a descriptive survey was developed to address the barriers to guideline-led prescribing in a middle-income setting.

Results

The literature review identified many gaps in knowledge in the Egyptian and Irish literature on HF. For instance, the studies included in the review did not discuss the target dose prescribing. The systematic review identified the widespread use of the Guideline Adherence Index (GAI-3) in 13 studies worldwide in the quantitative assessment of HF prescribing. The Irish HF outpatient study showed room for optimising the prescription of the guideline-directed medical therapies in 34% of ambulatory patients. No patient achieved the 100% target dose of all three evidence-based medications. The prevalence of potentially inappropriate prescribing was 20%. The Irish LTC study showed that patients with HF were older than those without HF (84.8 ± 7.4 vs 83.4 ± 7.9 years, *p-value = 0.024*). Loop diuretic was the most frequently prescribed HF medication up to 88% of the total population and renin-angiotensin system inhibitors to 24.2% only. The prevalence of potentially inappropriate prescribing in LTC was 24%. On the other hand, the Egyptian longitudinal study showed the moderate adherence level at discharge from the critical care unit but the potential role of clinical pharmacy service in HF drug therapy optimisation via improving beta-blocker prescription rates by from 24% to 38% and reducing digoxin rates from 34% to 23%. However, the service did not improve the overall guideline adherence levels or the prevalence of inappropriate prescribing. The survey explored some new

aspects in HF practice, such as the urgent need for locally-drafted guidelines and the more significant implementation of clinical pharmacy service to optimise the implementation of guideline-led prescribing in routine clinical practice.

Conclusion

This thesis has made a significant contribution to the knowledge and generated a much needed conceptual understanding of the complexity of HF guideline-led prescribing. This work reflects the moderate adherence levels to guidelines and high prevalence of potentially inappropriate prescribing in the two countries. None of the prescribers either in Ireland or Egypt prescribed at least a renin-angiotensin system inhibitor to all HF patients despite the strong, long-standing evidence.

1 Chapter 1
Introduction

This chapter provides a background to the thesis through an overview of the clinical presentation of Heart Failure syndrome, its aetiology, clinical epidemiology, management and economic burden. At the end of this chapter, the thesis rationale and design are described.

1.1 Heart Failure

Heart Failure (HF) syndrome is often the final and most severe manifestation of almost any form of cardiac diseases. [1, 2] According to the European Society of Cardiology (ESC), it is clinically defined as *"a syndrome in which patients have typical symptoms such as breathlessness, ankle swelling, and fatigue, and signs such as elevated jugular venous pressure, pulmonary crackles, and displaced apex beat, resulting from an abnormality of cardiac structure or function"*. [1]

Pathologically, HF is the inadequate pumping function of the myocardium such that the cardiac output is reduced relative to the metabolic demands of the body. [2, 3] Then, multiple hemodynamic and neurohormonal compensatory mechanisms occur in an attempt to compensate for the cardiac insufficiency. [2, 3] Once activated, these mechanisms lead to progressive deleterious consequences. [2, 3]

1.2 Left ventricular ejection fraction

Left ventricular ejection fraction (EF) is a parameter of ventricular remodelling and a reliable indicator of the myocardial pumping function. [4, 5] Ejection fraction is defined as the stroke volume, which is the end-diastolic volume minus the end-systolic volume, divided by the end-diastolic volume. [4, 5] Left ventricular EF is an essential marker of the progression of the myocardial disease as well as prognosis in HF patients. [4, 5] The lower the EF the patient has, the poorer the survival outlook for the patient. [4, 5] Most HF clinical trials select patients based upon their EF value. [6-8] According to the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012, HF is of two phenotypes: (i) HF with reduced ejection

fraction (HFrEF), also known as systolic HF; and (ii) HF with preserved ejection fraction (HFpEF), also known as diastolic HF. [9] In HFrEF, the ventricle contracts poorly and empties inadequately; and EF is < 50%. [9] In HFpEF, the ventricular filling is impaired, resulting in increased end-diastolic pressure at rest and/or during exercise; and EF is ≥ 50%. [9]

1.3 New York Heart Association classification

The New York Heart Association (NYHA) is a functional classification of HF severity that is widely used and accepted based on the patient's exercise capacity and severity of the disease symptoms. [1, 2] NYHA classifies HF patients into four grades as follows: [1]

(i) NYHA class I: No limitation on physical activity;
(ii) NYHA class II: Slight limitation on physical activities but comfortable at rest;
(iii) NYHA class III: Marked limitation on physical activities but comfortable at rest;
(iv) NYHA class IV: Inability to carry on any activity without symptoms, even at rest.

1.4 Main causes of Heart Failure

Heart Failure is a clinical syndrome rather than a complete diagnosis, and the underlying cause of the cardiac dysfunction should always be determined. [10] Internationally, the aetiology of HF is diverse. There is no agreed single classification system for the causes of HF, with much overlap between potential causes. [1, 10] Many patients will have several different pathologies - cardiovascular and non-cardiovascular - that lead to HF. [1, 10]

The major aetiologies are detailed in Table 1.1. Heart Failure is mainly a result of a diseased myocardium such as ischemic heart disease or abnormal loading conditions caused by hypertension or arrhythmias. [1, 2, 10] In the developed world, ischaemic heart disease and

hypertension remain the leading causes of HF. [11] There are little data for developing countries, but rheumatic heart disease continues to be a major health problem, particularly in Africa and Asia. [12-15] In African and African-American populations, hypertension remains the aetiology of HF in almost half of all cases. [16-18]

Table 1.1 Aetiology of Heart Failure.

I.	Coronary artery disease
II.	Intrinsic myocardial disease
	a. Dilated cardiomyopathy
	b. Hypertrophic cardiomyopathy
	c. Restrictive cardiomyopathy
III.	Valvular heart disease
	a. Age-related/calcific
	b. Infective endocarditis
	c. Immunological (e.g. rheumatic fever)
IV.	Congenital heart disease
V.	Hypertension
	a. Systemic hypertension
	b. Pulmonary hypertension
VI.	Arrhythmias and cardiac conduction disturbances
	a. Tachyarrhythmias
	b. Bradyarrhythmias
	c. Intraventricular conduction disturbance
VII.	High-output cardiac failure
	a. Anaemia
	b. Thyrotoxicosis
	c. Pregnancy
	d. Liver cirrhosis
	e. Paget's disease
VIII.	Pericardial disease
	a. Constrictive pericarditis
	b. Pericardial effusion with cardiac tamponade

Source: Cowie MR, Poole-Wilson PA. Pathophysiology of Heart Failure [10] and the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016. [1]

1.5 Clinical epidemiology of Heart Failure

1.5.1 Heart Failure epidemiology

The prevalence of HF is estimated to be 2% of the total adult population in the developed countries, rising to ≥ 10% among people of ≥ 70 years. [17] In total, there are 21 million adult patients estimated to be living with HF in Europe and the United States of America (USA). [17] Despite great advances in therapeutics, this number is expected to rise, partly due to the significant improvement of post-myocardial infarction survival rates, population ageing and the vast prevalence of cardiovascular risk factors worldwide. [19]

1.5.2 Heart Failure hospitalisation

Heart Failure accounts for 3% of all USA hospital admissions. In Europe, HF exacerbation is the leading cause of more than 1 million hospitalisations annually. [20] Also, rehospitalisation is common among patients with HF following their initial discharge. [21] The *Acute Decompensated HEart failure national REgistry* (ADHERE) in the USA reported a rehospitalisation rate of 22% in the first 30 days post-discharge. [22] Data from Europe showed a rehospitalisation rate of 44% in one-year post-discharge. [21, 23] It is of note that HF mortality risk increases considerably with repeated hospitalisations. [24]

The median length of hospitalisation for HF is typically between five and ten days. [21, 23] The length of stay reached a peak of 10 days in France. [21] However, the average length of stay tends to increase with patient age. [21] In England, the length of stay was five days for those < 65 years old and nine days for those > 85 years. [21]

1.5.3 Heart Failure mortality

Nearly 10% of HF patients die within 30 days of hospital discharge, 30% within the first year of diagnosis and 50% of HF patients die within five years. [25] The most recent European data demonstrates that 12-month all-cause mortality rates for hospitalised and ambulatory HF patients were 17% and 7%, respectively. [26] The *INTERnational Congestive Heart Failure* (INTER-CHF) registry showed that the overall one-year all-cause mortality in the Middle East is 9%, and in Africa, it is 34%. [27]

1.5.4 Patient quality of life

Heart Failure patient's quality of life is related to the frequency of hospitalisation and mortality. [21, 28, 29] Quality of life is subjective and does not merely reflect an objective clinical or physiological status. [28] Heart Failure patients' ability to work or to participate in social activities is significantly diminished. They are also more likely to suffer from other comorbidities such as depression, anxiety and social isolation. [21, 29] Work, travel and day-to-day social and leisure activities are difficult for those with breathlessness and extreme fatigue. [30-32] Worsening of the disease impacts not only the patient but also their caregivers. [33, 34] Studies have identified relatively high levels of deteriorating mental health and quality of life among partners of people with HF. [33, 34]

1.5.5 Economic burden of Heart Failure

Due to the high and increasing prevalence rates, HF constitutes an enormous economic burden for the healthcare systems in the developed countries. [35, 36] For example, Europe and the USA spend 1% to 2% of their annual healthcare budget on HF. [36] In 2014, the global economic

burden of HF was estimated at US$108 billion per annum, with US$65 billion attributed to direct costs and US$43 billion to indirect costs. [36] In the time period of 2004 to 2016, Europe accounted for 7% of the total global HF costs. [35, 36] For instance, estimates for the annual prevalence-based costs for HF patients ranged from US$868 in South Korea up to US$25,532 in Germany. [35, 36] In Europe, two-thirds of the HF budget was spent on hospital-related issues. [35, 36]

1.6 Heart Failure pathophysiology

Heart Failure represents a complex clinical syndrome in which an initial myocardial insult results in the over-expression of multiple peptides with different short- and long-term harmful effects on the cardiovascular system. [10, 37]

1.6.1 Renin-angiotensin-aldosterone system

Neurohormonal activation of the renin-angiotensin-aldosterone system (RAAS) is recognised as playing a pivotal role in the development as well as the progression of HF. [2] In the acute phase, the neurohormonal activation of renin, angiotensin-II and aldosterone seems to be beneficial in terms of maintaining adequate cardiac output and peripheral perfusion. [10] However, sustained neurohormonal activation eventually results in increased ventricular wall stress, dilation, and ventricular remodelling, as well as vasoconstriction. [10, 38] All these effects contribute to the disease progression in the failing myocardium, which eventually leads to further neurohormonal activation and fluid congestion. [10, 38] These effects will increase the heart rate (HR), which will further augment the metabolic demands and reduce the myocardium performance by increasing myocardial cell death. [2, 10, 38] Simultaneously, increased total

peripheral resistance results in higher afterload, impeding the left ventricle's stroke volume and reducing cardiac output. [2]

1.6.2 Left ventricular remodelling

Chronically elevated angiotensin-II and aldosterone trigger the production of cytokines, which activate macrophages and stimulate fibroblasts resulting in adverse ventricular remodelling. [2] Left ventricular remodelling is the process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape, and function. Its hallmarks include hypertrophy, loss of myocytes, and increased interstitial fibrosis. [39]

1.6.3 Natriuretic peptides

Natriuretic peptides are peptide hormones which regulate sodium-water balance, inducing natriuresis - the excretion of sodium by the kidneys. [10, 37] Several natriuretic peptides have been sequenced such as atrial natriuretic peptide and brain natriuretic peptide. [10, 37] The atrial natriuretic peptide is released from the atria in response to stretch, leading to natriuresis and vasodilatation. [40] Brain natriuretic peptide is also released from the heart, predominantly from the ventricles, and its actions are similar to those of atrial natriuretic peptide. [40] The atrial and brain natriuretic peptides increase in response to volume expansion and pressure overload of the heart and act as physiological antagonists to the effects of angiotensin-II on vascular tone, aldosterone secretion, and renal-tubule sodium reabsorption. [10, 37] These peptides participate in the long-term regulation of blood volume, arterial pressure, and sodium-water balance. [10, 37, 40] These potent vasodilatory peptides improve heart function and performance. [10, 37, 40] Also, they decrease the central venous pressure and increase the glomerular filtration rate at the renal level. [40] These vasoactive peptides are physiologically cleared by the enzyme

neprilysin endopeptidase. This clearance exacerbates HF progression and manifestations. [10, 37]

1.7 Pharmacological management of Heart Failure

Management of HF is complex and multifaceted. Pharmacotherapy is the cornerstone of HF management. [1] The medications used in HF block the adverse effects of the various neurologic, hormonal, and inflammatory mechanisms activated by the failing heart and relieve fluid congestion. [1]

1.7.1 Pharmacological options of Heart Failure management

Several medications have shown incremental benefits in HF syndrome. [41] These are:

(i) Angiotensin-converting enzyme (ACE) inhibitors to lower the arterial blood pressure (BP) and decrease the workload of the heart;
(ii) Beta-adrenergic blockers to stabilise and decrease the heartbeats;
(iii) Mineralocorticoid receptor antagonists (MRA) to reduce sodium retention and prevent myocardium remodelling;
(iv) Vasodilators to relax the smooth muscle lining of the veins and arteries;
(v) Digoxin cardiac glycoside to increase the strength of the myocardial contractility;
(vi) Ivabradine to reduce the HR;
(vii) Angiotensin receptor-neprilysin inhibitor (ARNi) to reduce remodelling, vasoconstriction, and renal sodium retention;
(viii) Diuretics to remove fluid congestion that is primarily manifested in the form of the ankle or pulmonary oedema.

The current therapeutic strategies are used to stabilise HF symptoms and progression. The main goals of therapy in HF patients are outlined in Table 1.2. [1, 21] Persistence of symptoms despite treatment usually indicates the need for intensification of therapy. [41] Oral HF therapy should

be continued on admission with acute HF, during and after hospitalisation, except in the presence of haemodynamic instability, hyperkalaemia or severely impaired renal function. [1, 9, 42] In these cases, the daily dosage of oral therapy may be reduced or stopped temporarily until the patient is stabilised. [1, 9]

1.7.2 Clinical practice guidelines

The ESC defines the clinical practice guidelines as *"systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"*. [1] The National Cardiac Societies of the ESC are encouraged to endorse, translate and implement all ESC guidelines. [1, 9] Implementation programmes and audits are recommended because it has been shown that the precise application of clinical recommendations may favourably influence the outcome of the syndrome. [1, 43, 44]

A great number of guidelines have been issued in recent years by the ESC as well as by other societies and organisations such as the American College of Cardiology, American Heart Association, Heart Failure Society of America [43], National Institute for Health and Care Excellence in the United Kingdom [45], and National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand [44].

Concurrently, the ESC Task Force and the working groups of American College of Cardiology, American Heart Association, Heart Failure Society of America separately surveyed the evidence, arrived at similar conclusions, and constructed similar recommendations in 2016. [1, 43] Given the concordance, the respective organisations simultaneously issued aligned

recommendations on the use of these new treatments to minimise confusion and improve the care of patients with HF. [1, 43]

Table 1.2 Goals of therapy in patients with established Heart Failure diagnosis. [1, 21]

Relieve symptoms and signs such as oedema and low-cardiac output
Restore normal oxygenation
Optimise volume status
Identify aetiology
Identify and manage potential precipitating factors and comorbidities
Initiate or optimise chronic Heart Failure guideline-directed medical therapies
Minimise side effects
Achieve target blood pressure and target heart rate
Avoid prescription of potentially harmful medications

1.7.3 Guideline-led prescribing

Guideline-led prescribing refers to the appropriate prescription of the drug treatments that benefit patients with HF, and it evokes the body of evidence-based literature and the endorsement of several professional societies. [46-48] Guideline-led prescribing, which is the appropriate prescription of the guideline-directed medical therapies, represent the mainstay of initial and chronic management of HF. [1, 49] The cornerstone of guideline-led prescribing is the prompt initiation of the inhibitors of the RAAS and the evidence-based beta-blockers (EBBB) shown to improve symptoms, cardiac function, morbidity and mortality. [41, 49]

1.7.4 Guideline-recommended target dose

The target dose is defined as the dose that achieves a recommended target effect of the study medication over placebo. [50] In HF, the ESC guidelines strongly recommend the uptitration of guideline-directed medical therapies to the evidence-based levels in order to achieve the full beneficial outcomes of medications. [1, 47, 48]

1.7.5 Differences between ESC 2012 and 2016 guidelines

The major changes from the 2012 guidelines relate to: [1, 9]

(i) A new term for patients with HF and a left ventricular EF that ranges from 40 to 49% — 'HF with mid-range EF (HFmrEF)'

(ii) A new algorithm for the diagnosis of HF in the non-acute setting based on the evaluation of HF probability;

(iii) Recommendations aimed at prevention or delay of the development of overt HF or the prevention of death before the onset of symptoms;

(iv) Indications for the use of the new compound sacubitril/valsartan, the first in the class of ARNi (Figure 1.1 vs Figure 1.2);

(v) The concept of early initiation of appropriate therapy along with relevant investigations in acute HF that follows the 'time to therapy' approach already well established in acute settings.

1.7.6 Management of Heart Failure with reduced ejection fraction

The ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic HF in 2012 (Figure 1.1) and 2016 (Figure 1.2) recommend the utilisation of up to seven disease-modifying agents in addition to the diuretic therapy for managing HFrEF. [1, 9] The incremental use of combinations of disease-modifying agents has resulted in the progressive improvement in mortality and hospitalisation outcomes in HFrEF. [41] In the case of de-novo HFrEF presentation, every attempt should be made to initiate these agents after haemodynamic stabilisation. [1, 9] In the case of worsening chronic HFrEF, every attempt should be made to continue the guideline-directed disease-modifying therapies, in absence of haemodynamic instability or contraindications. [1, 9, 42]

1.7.6.1 Pharmacological options recommended in all symptomatic patients with Heart Failure with reduced ejection fraction

ACE inhibitors have been shown to decrease HF morbidity and mortality and should be given to all patients with left ventricular dysfunction, symptomatic or otherwise unless there is a contraindication or prior intolerance to therapy. [51-53] Several trials showed the significant benefits of ACE inhibitors in reducing all-cause mortality between 10% to 40% and HF hospitalisation by 15% over a mean follow-up period of 0.5 to 3.8 years. [51-53]

Evidence-based beta-blockers have also been shown to decrease the morbidity and mortality associated with HF. [1, 41] The EBBBs are bisoprolol, carvedilol, metoprolol succinate,

nebivolol. They should be initiated at low doses and titrated upwards target doses. [1, 9] Although adverse drug reactions can include bradycardia, worsening of reactive obstructive lung diseases, and worsening HF, these can often be avoided by the careful patient selection, appropriate selection of the agent, gradual dose titration, and close monitoring. [1] Clinical improvement may be delayed and may take two to three months to become apparent. However, the persistent long-term treatment with EBBB lessens HF symptoms and significantly improves the clinical outcomes such as all-cause mortality by 35%. [54-57] A meta-analysis of observational studies and clinical trials demonstrated that discontinuation of EBBB in patients hospitalised with acute HF was associated with significantly increased in-hospital mortality, short-term mortality and the combined endpoint of short-term rehospitalisation or mortality. [42]

Mineralocorticoid receptor antagonists such as spironolactone and eplerenone are recommended in HF patients who are in NYHA class II to IV unless contraindicated. [1] The *Randomized Aldactone Evaluation Study* (RALES) trial showed a reduction of 30% in mortality and 35% in rehospitalisation among the patients in the spironolactone arm versus those in the placebo arm. Similarly, the *Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure* (EMPHASIS-HF) trial showed a significant reduction in all-cause mortality by 24% and HF hospitalisation rate by 42%. [58]

1.7.6.2 Other pharmacological options recommended in selected symptomatic patients with heart failure with reduced ejection fraction

Angiotensin-II receptor blockers (ARBs) are a reasonable alternative to ACE inhibitors in all patients with HFrEF or HFpEF who are intolerant of ACE inhibitors because of cough or angioedema. [(1)] Experience with this medication class in controlled clinical trials of patients with HF is considerably less than that with ACE inhibitors. [(1)] Nevertheless, valsartan and candesartan have demonstrated a similar reduction in hospitalisations and mortality compared to ACE inhibitors. [(59-61)] Overall, several clinical trials of ARBs have shown a significant decrease in combined cardiovascular mortality and HF hospitalisation by 3.2% up to 15% over 1.9 years to 3.4 years. [(59-61)]

Angiotensin receptor-neprilysin inhibitors are a novel class of HF medical therapy consisting of a combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB. [(7)] In the *Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure* (Paradigm-HF) trial, sacubitril/valsartan was superior to enalapril in reducing mortality and HF hospitalisation in HFrEF. [(7)] In 2015, the drug combination was approved in Europe and the USA for the treatment of HFrEF, and it is included in the ESC 2016 guidelines (Figure 1.2). [(1, 7)] In these guidelines, ARNi is recommended as a replacement for an ACE inhibitor therapy to further reduce the risk of HF hospitalisation and mortality in ambulatory patients with HFrEF who remain symptomatic despite optimal medical therapy with an ACE inhibitor, an EBBB and an MRA at target dose or maximally tolerated dose. [(1)] Compared to the established therapy of ACE inhibitor, ARNi is an expensive therapy. Although this agent was licenced in Ireland, it was not approved for use on the Primary Care Reimbursement Service dispensing schemes until December 2017. [(62)] It must be initiated by a cardiologist, and the cardiologist must complete an online form to justify its use. For this

reason, the use of ARNi has been limited in Ireland up to this time. [62] Similarly, the use of this medication class is minimal in Egypt due to its cost implications since its introduction in the Egyptian market in October 2017.

Ivabradine slows the HR through inhibition of the mixed sodium-potassium (I*f*) channel in the sinus node and therefore should only be used for patients in sinus rhythm. [8] In the *Systolic Heart failure treatment with the* I*f inhibitor ivabradine* (SHIFT) clinical trial, ivabradine reduced the combined endpoint of mortality and hospitalisation by 18% for symptomatic HF patients with EF ≤ 35%, who were in sinus rhythm, with a HR ≥ 70 beats per minute, who had been hospitalised for HF within the previous 12 months, and who were receiving optimal medical therapy with the target dose of EBBB (or maximally tolerated dose), ACE inhibitors (or ARB), and an MRA. [1, 8]

Digoxin can be beneficial in patients with current or prior symptoms of HF, especially those with comorbid atrial fibrillation. [1, 9, 63] When added to ACE inhibitors, beta-blockers, and diuretics, digoxin can reduce symptoms, prevent hospitalisation, control rhythm, and enhance exercise tolerance. [63] In recent years, the use of digoxin has diminished as newer therapies demonstrated more significant survival benefits (Figure 1.1 and Figure 1.2). [1, 9, 64]

Vasodilators such as hydralazine and isosorbide dinitrate combination may be a useful therapeutic alternative in patients intolerant to both ACE inhibitors or ARB. [65] The *African American Heart Failure Trial* (A-HeFT) showed that this therapy was of particular effectiveness in African American HF patients. [66]

Diuretics should be used in all HF patients with symptoms or signs of congestion, irrespective of their EF. [1, 67] Loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF as they produce a more intense and shorter diuresis than other classes of diuretics. [1] Careful monitoring of renal function and electrolytes is essential. [1] The lowest therapeutic dose of diuretic should be used to relieve congestion, keep the patient asymptomatic, and maintain a dry weight. [67, 68] In the case of resistant congestion, the addition of a second diuretic of different mechanism of action is required. [69] The combinations of loop and thiazide diuretics act synergistically and may be used to treat resistant oedema. [1] However, adverse effects are more likely, and these combinations should only be used with care. Diuretic therapy should aim to achieve and maintain euvolemia with the lowest achievable dose. [1]

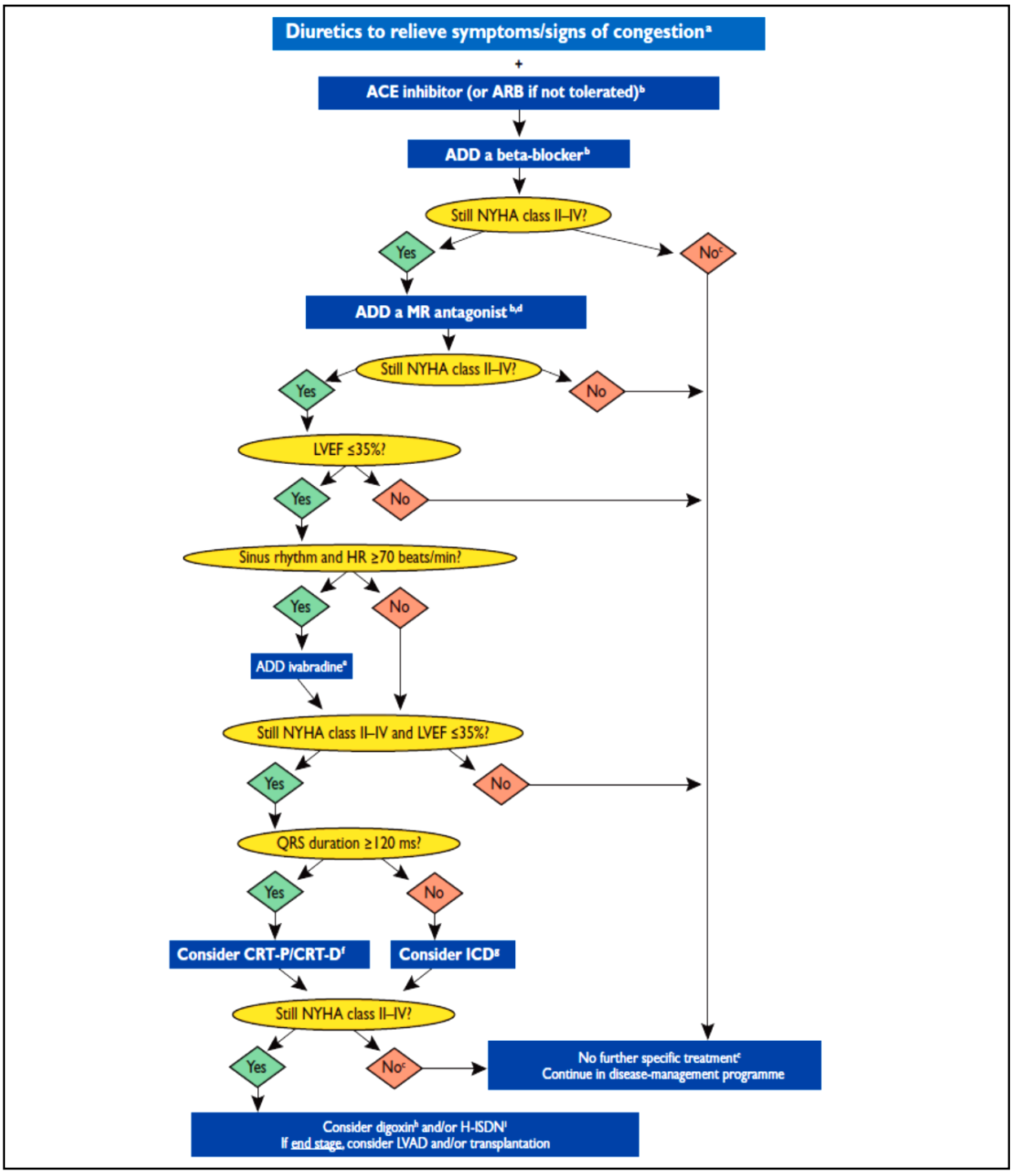


Figure 1.1 Management algorithm of Heart Failure with reduced ejection fraction in the European Society of Cardiology Heart Failure guidelines 2012.

Source: European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, 2012. [9] **Abbreviations:** ARB, angiotensin-II receptor blocker; CRT-D, Cardiac Resynchronization Therapy-Defibrillator; CRT-P, Cardiac Resynchronization Therapy-Pacemaker; H-ISDN, hydralazine-isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter-defibrillator;

LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MR, mineralocorticoid receptor; NYHA, New York Heart Association.

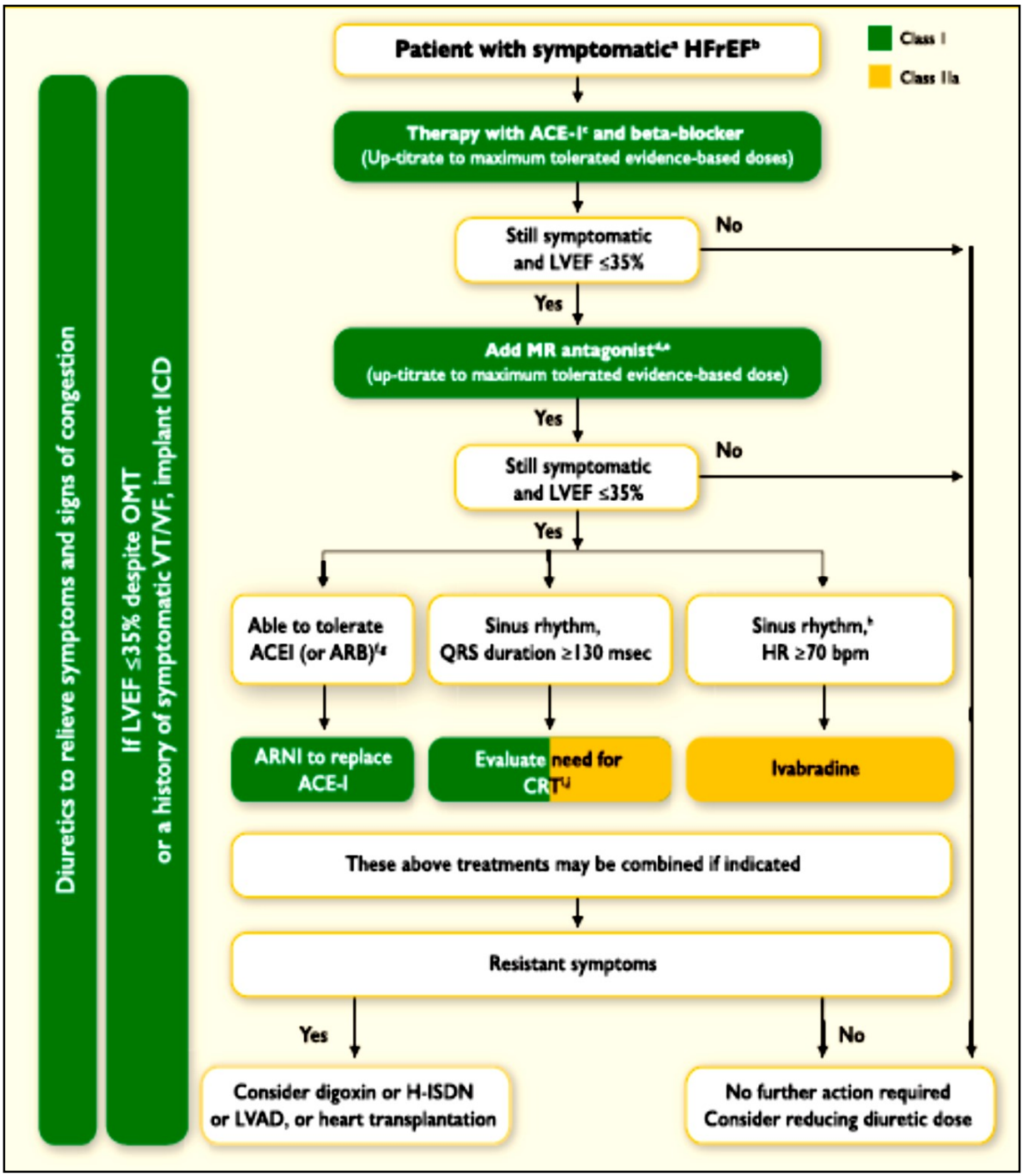


Figure 1.2 Management algorithm of Heart Failure with reduced ejection fraction in the European Society of Cardiology Heart Failure guidelines 2016.

Source: European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, 2016. [(1)]

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNi, angiotensin receptor - neprilysin inhibitor; CRT, cardiac resynchronization therapy;

HFrEF, heart failure with reduced ejection fraction; H-ISDN, hydralazine-isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; MR, mineralocorticoid receptor; NYHA, New York Heart Association; OMT: optimal medical therapy; VT/VF, ventricular tachycardia/ventricular fibrillation..

1.7.7 Management of Heart Failure with preserved ejection fraction

There are no specific disease-modifying agents currently recommended for this cohort of HF patients as no treatment has been shown to reduce the disease mortality. [6, 70-72] However, in older patients ≥ 70 years with HFrEF or HFpEF, nebivolol reduced the combined endpoint of mortality or cardiovascular hospitalisation by 14% regardless of the EF level in comparison to placebo. [57]

In clinical practice, all the aforementioned pharmacological options (section 1.7.6) are used in stabilising HFpEF signs and symptoms and preventing its progression, as well as the management of the cardiovascular comorbidities. [6, 72-74] The guidelines suggest the utilisation of the same medications for managing cardiovascular comorbidities and HFpEF symptoms. [1, 9]

The *Candesartan cilextil in Heart Failure Assessment of Reduction in Mortality* (CHARM-PRESERVED) trial of HFpEF patients showed a significant 2.4% decrease in the HF hospitalisation rate in the candesartan arm versus the placebo arm over three years of follow-up. [75] Similarly, the *Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist* (TOPCAT) clinical trial showed a significant 2.2% reduction in HF hospitalisations in the spironolactone arm in comparison to the placebo arm. [6] A sub-analysis of the TOPCAT trial found a significant reduction in all-cause mortality in the arm of the American HFpEF patients in comparison to the arm of Latin American and Russian patients. [6]

1.7.8 Benefits of guideline-directed medical therapies

Guideline-led prescribing leads to many clinical and economic benefits, including:

(i) Reduction of hospitalisation and rehospitalisation frequency; [46-48, 76, 77]
(ii) Shortening of hospital length of stay; [46, 78]
(iii) Improvement of survival; [47, 48, 76, 79]
(iv) Reduction of adverse cardiovascular events; [46, 79, 80]
(v) Decrease of mechanical ventilation needs; [1, 78, 80, 81]
(vi) Improvement of patient's quality of life. [78, 81, 82]

Robust evidence demonstrates the strong association between guideline-led prescribing of the evidence-based medications and improved survival as well as the patient's quality of life. [1, 21, 48, 76] In the *BIOlogy Study to Tailored Treatment in Chronic Heart Failure* (BIOSTAT-CHF) and *QUality of Adherence to guidelines' recommendations for LIFe-saving treatment in heart failure survey* (QUALIFY) registries, the optimisation of HF medications and prescription of ≥ 50% of the guideline-recommended target doses demonstrated considerable benefits in terms of survival and rehospitalisation outcomes in the short and long term. [48, 76] In the QUALIFY registry, perfect adherence to guideline-led prescribing was significantly associated with a 50% reduction in all-cause mortality and a 32% reduction of HF-related rehospitalisation when compared to moderate or poor adherence levels. [47, 48]

The majority of international registries show that HF management in routine clinical practice is not well aligned with the recommendations of the clinical practice guidelines (Table 1.3). Adherence to HF guideline-led prescribing is highest in North America, Western Europe, and Japan and lowest in Eastern Europe, Africa and Asia. [83] The pilot study of the European Long-Term Registry (ESC – HF Pilot) showed significant differences in the management of HF across European countries, resulting in different 1-year clinical outcomes. [26] *The Sub-Saharan*

Africa Survey on Heart Failure (THESUS-HF) registry showed underutilisation of beta-blockers in the Middle-East and Africa in comparison to populations from Western regions. [12]

The guidelines strongly recommend, and the optimal clinical outcomes are achieved with the target dosing of guideline-directed medical therapies. [41, 84] The *Assessment of Treatment with Lisinopril And Survival* (ATLAS) and the *Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure* (HEAAL) clinical trials emphasised the significant benefits of renin-angiotensin system inhibitors (RASi) target dose prescribing in comparison to lower doses in terms of mortality or rehospitalisation. [53, 85] Medication dosing should target the evidence-based levels to improve heart function, and should not be based on specific BP readings or established symptom relief. [1] However, the most recent registries of contemporary ambulatory HF patients such as the American *CHAnge the Management of Patients with Heart Failure* (CHAMP-HF) [86], the European BIOSTAT-CHF [76] and the Dutch *Chronic Heart failure ESC guideline-based Cardiology practice Quality project* (CHECK-HF) [87] revealed a persistent gap between the guidelines' recommendations and the actual utilisation rates of the guideline-recommended target doses. For instance, in CHAMP-HF registry, only 1% of eligible patients achieved the target dose of all three guideline-directed medical therapies, that are RASi, EBBB and MRA despite the absence of contraindications. [86]

Table 1.3 The prescription rates of Heart Failure medications in international registries from 2005 to 2016, N = 9.

Registry Name	Country/Continent	Publication year	Number of patients	RASi, %	Beta-Blockers, %	Mineralocorticoid receptor antagonists, %	Digoxin, %	Diuretics, %
ADHERE [22]	USA	2005	107,362	89	48	*N/A*	28	70
EHFS II [88]	Europe	2006	3,508	82	61	48	31	90
OPTIMIZE-HF [89]	USA	2008	4,402	68	67	*N/A*	*N/A*	*N/A*
IMPACT-RECO II [90]	France	2009	1,907	98	70	35	19	85
ESC – HF Pilot [23]	Europe	2010	1,855	89	87	55	20	83
I-PREFER [91]	L-MICs	2011	699	95	71	52	39	74*
THESUS-HF [12]	Africa	2012	1,006	82	28	72	62	80*
GET WITH THE GUIDELINE [92]	USA	2013	99,930	52	52	11	16	65
QUALIFY [93]	36 countries	2016	7,092	87	87	69	25	83

*Loop diuretics only.

Abbreviations: ADHERE, Acute Decompensated Heart Failure National Registry; EHFS II, European Heart Failure Survey II; ESC-HF, European Society of Cardiology – Heart Failure Long-Term Registry; I-PREFER, Identification of Patients With Heart Failure and PREserved Systolic Function: an epidemiological regional study; L-MICs, Low-Middle Income Countries; N/A, not available or not reported; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; QUALIFY, QUality of Adherence to guidelines' recommendations for LIFe-saving treatment in heart failure survey; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker); THESUS-HF, The Sub-Saharan Africa Survey of Heart Failure; USA, the United States of America.

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1.7.9 Therapeutic contraindications to the guideline-directed medical therapies

The ESC 2016 guidelines defined a list of relative and absolute contraindications as specific situations in which the HF recommended medication should not be used because it may be harmful to the particular patients. [1] The ESC guidelines outlined the presence or the previous history of a drug-specific allergic reaction as a general absolute contraindication to all medications mentioned above. [1]

1.7.9.1 Contraindications to renin-angiotensin system inhibitors (ACE inhibitor, ARB and ARNi)

- History of angioedema.
- Known bilateral renal artery stenosis.
- Pregnancy/risk of pregnancy.

1.7.9.2 Contraindications to evidence-based beta-blockers

- Second or third-degree atrioventricular block (AV-block).
- Critical limb ischaemia.
- Asthma (relative contraindication).

1.7.9.3 Contraindications to ivabradine

- Unstable cardiovascular conditions (acute coronary syndrome, stroke/transient ischaemic attack, severe hypotension).
- Severe liver dysfunction or renal dysfunction (no evidence on safety or pharmacokinetics for creatinine clearance < 15 mL/min).
- Pregnancy or breastfeeding.

1.8 Potentially inappropriate prescribing in Heart Failure

Medications are considered to be appropriately prescribed when they have a clear evidence-based indication, are cost-effective and are well tolerated. [94] Potentially inappropriate prescribing is defined by the American Institute of Medicine as *"the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist".*[94-96] Unlike contraindications, potentially inappropriate prescribing introduces the risk of an adverse drug event which has the potential to outweigh the medication's clinical benefit, mainly when a safer or more effective alternative treatment option is available. [97]

Comorbidities and multimorbidity frequently accompany the HF syndrome, leading to therapeutic complexity, treatment conflicts and high prevalence of potentially inappropriate prescribing. [98-101] In HF setting, potentially inappropriate prescribing refers to the medications or medication classes that are not recommended in symptomatic patients with HF. [102] This type of prescribing is believed to cause harm or contradict the effects of the HF guideline-directed medical therapies. [1, 102] Well described examples of this harmful interaction are non-steroidal anti-inflammatory drugs (NSAIDs), non-dihydropyridine calcium channel blockers (CCB) and thiazolidinediones. [1, 102]

In a Danish nationwide population of 36,354 ambulatory HF patients prescribed NSAIDs, Gislason *et al.* found that NSAIDs significantly increased the mortality rate by 70% regardless of the dose. [103] They also found a dose-dependent increase in the risk of mortality and cardiovascular hospitalisation. [103] Elsewhere, a meta-analysis of observational studies and randomised controlled trials showed the harmful effects of NSAIDs on HF patients in terms of prognosis and clinical outcomes. [104]

Non-dihydropyridine CCBs are not indicated for the treatment of patients with HF. Diltiazem and verapamil are unsafe in patients with HF due to their potent negative inotropic effects. [1] In a study of 2,466 patients with recent myocardial infarction randomised to diltiazem or placebo, diltiazem significantly increased the risk of adverse cardiac events (hazard ratio [HR], 1.41; 95% confidence intervals [CI], 1.01–1.96). The risk of adverse cardiac events in patients receiving diltiazem was directly related to the severity of baseline HF in the subgroup of 490 patients with baseline pulmonary congestion. [105]

Furthermore, the *Diabetes Reduction Assessment with ramipril and rosiglitazone Medication* (DREAM) trial, which evaluated rosiglitazone versus placebo in patients at risk for type 2 diabetes mellitus, demonstrated the higher frequency of HF onset in those patients treated with rosiglitazone (n = 2,635) compared with placebo (HR, 7.03; 95% CI, 1.60 – 30.9; *p-value = 0.01*). [106] Another example of an HF potentially inappropriate medicine is the antifungal agent itraconazole which has been associated with occasional reports of cardiotoxicity, and new-onset and worsening HF due to its negative inotropic effect. [107, 108]

The ESC 2016 guidelines address the point of potentially inappropriate prescribing in the form of potential drug interactions that may result in lower efficacy, poorer safety, the occurrence of unfavourable side effects, or worsening HF. [1] The guidelines mentioned NSAIDs, thiazolidinediones, non-dihydropyridine CCBs, and beta-2 agonists as therapeutic conflicts with the guideline-directed medical therapies in HF patients. [1]

However, the literature about potentially inappropriate prescribing towards HF patients in routine clinical practice is very scarce. [98, 99, 101] Heart Failure-specific potentially inappropriate

prescribing was marginally part of many explicit prescribing review tools of potentially inappropriate medications in older individuals such as the Screening Tool of Older Person's Prescriptions / Screening Tool to Alert doctors to Right Treatment (STOPP/START) or Beer's criteria. [94, 96, 97, 109-111]

The first HF-specific potentially inappropriate prescribing review tool was designed by the St. Vincent's University Hospital, Dublin, using the Delphi technique. [112] The St. Vincent's Potentially Inappropriate Medicines in Heart Failure (PIMHF) tool included 11 medications or medications' classes that are deemed harmful to HF prognosis or clinical outcomes (Appendix 1). [112] In 2016, Page *et al.* published the first scientific statement for potentially inappropriate medications in HF patients. [102] The purpose of the scientific statement was to assist prescribers in improving the quality of care for patients with HF, potentially reducing hospital admissions, improving quality of life for patients with HF, and reducing healthcare costs. [102] The statement is a comprehensive list included medications or medications classes that may cause, exacerbate HF prognosis or limit the beneficial effects of the guideline-directed medical therapies. [102]

1.9 Rationale of work

Heart Failure is a major cause of mortality, morbidity and impairment of patient's quality of life and places a substantial financial burden on healthcare systems worldwide. [17] International guidelines make clear recommendations as to which evidence-based medications should be prescribed for patients with HF. [1] However, observational studies from national and international registries have repeatedly shown that patients are missing out on guideline-directed medical therapies. [47, 76, 86, 87, 113] Even when prescription rates are high, patients frequently fail to reach the target doses. The guidelines strongly recommend, and the optimal patient outcomes are achieved, with the prescription of the recommended target doses of HF therapies. [41, 84]

The HF syndrome is accompanied by a broad spectrum of both cardiovascular and non-cardiovascular comorbidities. [100, 114] Thus, patients with HF often have a high medication burden consisting of complex dosing regimens and problematic polypharmacy. [115, 116] On average, HF patients take 6.8 prescription medications per day, resulting in 10.1 doses per day. [102] Drugs may cause or exacerbate HF by causing direct myocardial toxicity; by negative inotropic, lusitropic, or chronotropic effects; by exacerbating hypertension; by altering serum electrolyte levels; or by drug-drug interactions that limit the beneficial effects of HF medications. [1, 112]

To our knowledge, the current literature lacks a combined assessment of HF-specific appropriate and potentially inappropriate prescribing in the same clinical settings to establish all possible opportunities for improving prescribing practice.

1.10 Aims and Objectives

1.10.1 The aims of this thesis:

This thesis has a twofold aim:

Firstly, to assess guideline-led prescribing of the evidence-based HF medications and to identify the potential barriers to guideline-led prescribing in routine clinical practice in Ireland and Egypt;

Secondly, to assess the prevalence of HF-specific potentially inappropriate prescribing and the relationship between potentially inappropriate prescribing and guideline-led prescribing, if any, in Irish and Egyptian settings.

1.10.2 Study objectives

Specifically, the objectives are to:

Review the published literature in Ireland and Egypt regarding HF prescribing practices and utilisation of HF pharmacotherapy. This objective will be covered in Chapter 2.

Identify the objective tools for assessing adherence to guideline-led prescribing in HF and to assess the clinical outcomes associated with guideline adherence measured by such tools. This objective will be addressed in Chapter 3.

Evaluate the guideline-led prescribing and potentially inappropriate prescribing to contemporary HF patients in an Irish ambulatory setting. This objective will be addressed in Chapter 4.

Measure guideline-led prescribing and potentially inappropriate prescribing in the Irish Long-Term Care facilities and identify the clinical factors associated with guideline-led prescribing in this vulnerable HF population. This objective will be covered in Chapter 5.

Assess guideline-led prescribing towards HF patients at discharge from a critical care setting and assess the effect, if any, of the introduction of clinical pharmacy service in this setting. This objective will be addressed in Chapter 6.

Explore the behaviours and perspective of physicians towards prescribing to HF patients at discharge from a critical care unit and investigate the potential barriers and solutions to HF guideline-led prescribing in this Egyptian setting. This chapter will be covered in Chapter 7.

1.11 Thesis outline

Each of the six objectives outlined above is aligned to a specific study chapter (Chapter 2 – 7), and each of these chapters is either published in an international peer-reviewed journal or drafted for submission. The six study chapters are then followed by an overall discussion chapter (Chapter 8). The methods used in this thesis and the resultant findings are discussed separately in each of the six study chapters (Figure 1.3). In brief, the outline for the remainder of this thesis is as follows:

Chapter 2: A narrative literature review of HF prescribing in Ireland and Egypt to identify the gaps in knowledge in each country.

Chapter 3: A systematic review and meta-analysis of the objective tools for assessing the quality of HF guideline-led prescribing and the outcomes of guideline-led prescribing.

Chapter 4: A prospective observational study of guideline-led prescribing in a cohort of HF ambulatory patients, in the Mercy University Hospital, Cork City, Ireland.

Chapter 5: A retrospective multicentre observational study of the level of HF appropriate and potentially inappropriate prescribing among the older patients residing in Long-Term Care facilities in Cork City and County, Ireland.

Chapter 6: A quantitative analysis of guideline-led prescribing in hospitalised HF patients and assessment of the quality of care before and after the implementation of clinical pharmacy service in the Critical Care Unit, Cairo University Hospitals, Egypt.

Chapter 7: A descriptive survey exploring the perspective of prescribers towards HF patients in a critical care setting and identifying the barriers to the guideline-led prescribing in the Critical Care Medicine Department, Cairo University Hospitals, Egypt.

Chapter 8: An overall discussion of the research, including the strengths and limitations with suggestions for future research and implications for policy and practice.

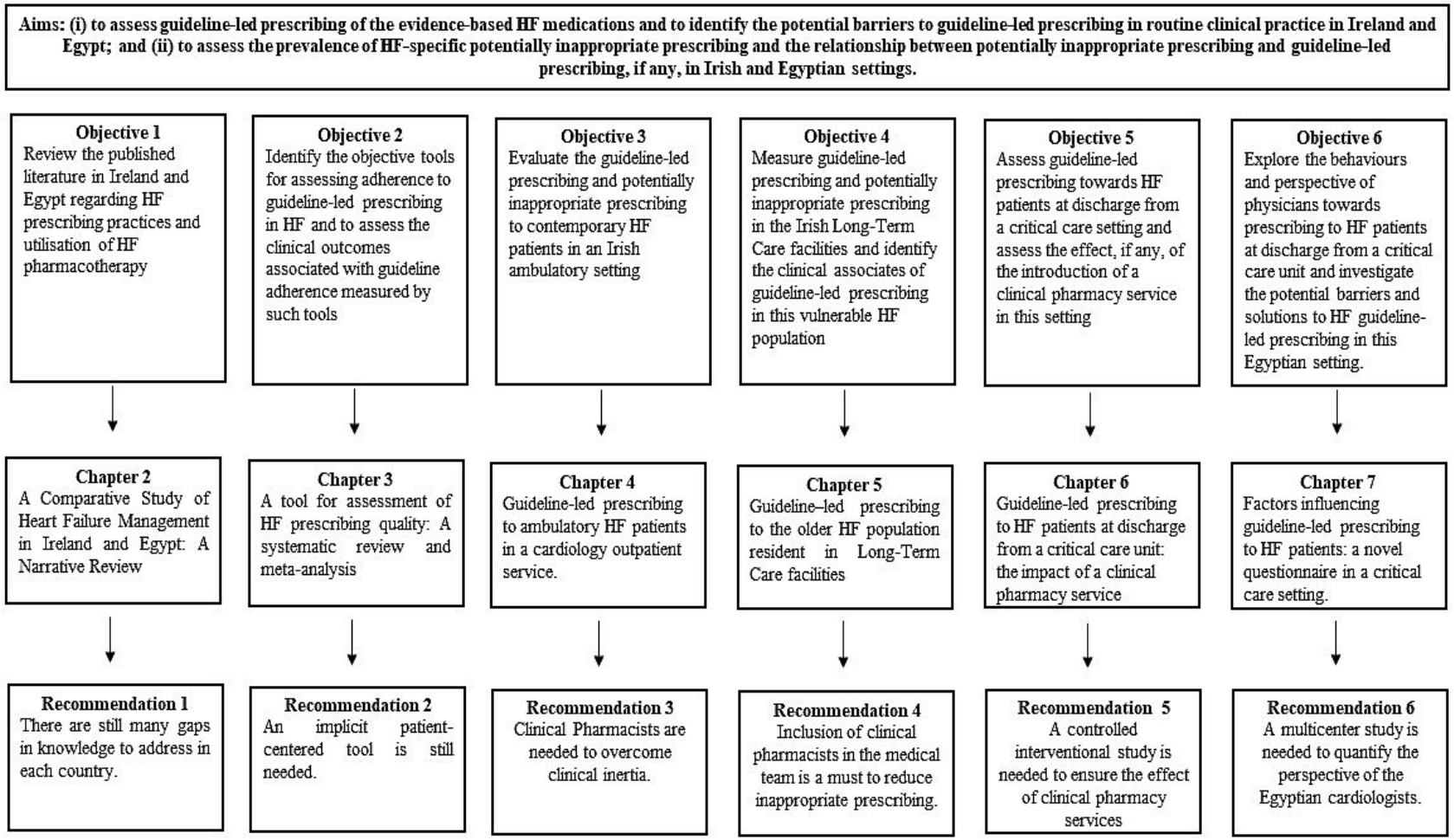


Figure 1.3 Thesis Chapters and Recommendations.

2 Chapter 2

A Comparative Study of Heart Failure Management in Ireland and Egypt: A Narrative Review

This chapter provides a narrative literature review on Heart Failure management in Ireland as a developed European country and Egypt as a developing Middle-Eastern country. This literature review aims to identify the gaps in knowledge about Heart Failure management in either country. Based on this literature review, the rationale of the future work, and the thesis aim, objectives and structure were outlined.

2.1 Introduction to the healthcare system in Ireland and Egypt

Ireland is a Western European country with a population of 4.85 million people in 2018. [117, 118] The Irish Gross National Income per capita is USD 59,360, and 0.2% of the population are below the poverty line of USD 1.9 per day. The average life expectancy in Ireland is 82 years old. [117, 118] In 2010, Ireland spent €2,862 per capita on health, compared to a European Union average of €2,172 per capita. Of this spending, approximately 79% was governmental expenditure. [117, 118] According to the Irish Central Statistics Office, health expenditure in 2015 was €19.9 billion, representing 7.8% of the country's Gross Domestic Product. In 2013, the ratio of hospital beds to the population was estimated to be 28: 10,000. [117, 118]

Ireland has a comprehensive, government-funded public healthcare system. [119] The Irish healthcare system is two-tier: public and private sectors. The public health care system is governed by the Health Act 2004, which established a new body to be responsible for providing health and personal social services to everyone living in Ireland – the Health Service Executive. [119] The new national health service came into being officially on 1 January 2005; however, the new structures are currently in the process of being established as the reform programme continues. In addition to the public sector, there is also a large private healthcare market. [119]

According to a national report about HF costs in Ireland published in 2015 by the Irish Heart Foundation, 90,000 Irish people are living with HF, and there are another 160,000 asymptomatic HF cases in Ireland. [120] The report mentioned that in 2013, the rehospitalisation rates ranged from 24% to 44%, where 50% of patients are readmitted within six months of discharge, and the estimated length of stay is 11 days. The mortality rates are estimated to be 8% in the first-month post-discharge and 60% to 70% within the first five years post-diagnosis.

[120] According to this national report, the total annual cost of HF in Ireland is estimated to be €660 million per annum. This cost is mainly driven by hospitalisation that consumes 47% of the total annual cost of HF care in Ireland while 16% of the cost is spent on HF medications. The total cost of inpatients hospitalisations for the year 2012 was estimated at €43 million. The cost of community-based pharmacological management of HF patients was estimated to be €26 million, and the annual drug cost per patient was estimated to be between €194 and €290 per annum based on 2012 figures. [120]

On the other hand, Egypt is a Middle-Eastern North African (MENA) country with a population of 98.42 million. [117, 118] In 2018 the Egyptian Gross National Income per capita was USD 275.41 billion, in and [117, 118] 1.2% of the population were below the poverty line of USD 1.9 per day. The average life expectancy in Egypt is 72 years old. In 2014, the total expenditure of Egypt on health per capita was $594. [117, 118] and total expenditure on health represented 5.6% of the country Gross Domestic Product (GDP). In 2015, the ratio of hospital beds to the population was estimated to be 16: 10,000. [117, 118]

The healthcare system in Egypt consists of both public and private sector. Public health coverage is offered through the Ministry of Health and Population, which operates a series of medical facilities providing free health services. [121-124] The parastatal sector is composed of quasi-governmental organizations in which government ministries have a controlling share of decision making, including the Health Insurance Organization, the Curative Care Organization, and the Teaching Hospitals and Institutes Organization as well as the teaching hospitals of the state universities. [121-125] The former two organisations are the largest healthcare organizations in Egypt. The Health Insurance Organization covers employed persons, students, and widows

through premiums deducted from employee salaries and employer payrolls. It operates its own network of medical facilities and at times contracts with private healthcare providers. The Curative Care Organization operates in specific governorates, and contracts with other entities for the provision of care. There are also private insurance options and a network of private healthcare providers and medical facilities. In addition, many Islamic mosques also operate their own clinics, especially in the large cities and also, some Christian churches offer subsidised or free clinics. [121-125]

The exact prevalence of HF in Egypt is unknown; however, the disease emerges a decade younger in MENA regions than in Europe and the USA. [13, 16] The available MENA data suggest that HF patients are more likely to be in NYHA class IV due to the delayed diagnosis or the late presentation to the healthcare settings in comparison to patients from the Western countries. [12, 27] Data from the Egyptian National Hypertension Project were collected between 1990 and 1993 and estimated the national incidence rate of HF as 300 cases per 100,000 persons. [121] This rate was significantly higher than that of breast cancer and cervical cancer that had incidence rates of 54 cases per 100,000 and 24 cases per 100,000, respectively, at that time in Egypt. The project estimated the national prevalence of HF up to 11% of the Egyptian population according to Framingham diagnostic criteria. [121, 126] The project results also showed that 50% of Egyptian HF patients die within four years of the diagnosis, while 50% of patients with severe HF die within the first year of diagnosis. [121]

2.2 Aim

The aim of conducting a detailed narrative literature review for this thesis is to explore and evaluate the existing evidence base for studies investigating HF pharmacotherapy in Ireland

and Egypt as a comparative study between a European country of high-income and a Middle Eastern country of middle income.

2.3 Method

A search was performed in Medline, Scopus, EMBASE, and Google Scholars databases without a restriction to date or language. The following search terms were used: 'heart failure', 'guidelines', 'guideline adherence', 'guideline compliance', 'physician prescribing pattern', 'Ireland', and 'Egypt' used either single or combined terms as Boolean logic and MeSH terms. The search was supplemented by searching databases of grey literature (associations, organizations and government reports) and reference lists and was not limited by dates of publication. For building a comprehensive and complete coverage about HF in Egypt, relevant researchers from the Egyptian Society of Cardiology (EgSC) and Novartis Medical Information Office were contacted by email. [127] The online research network www.researchgate.net was also searched.

Inclusion criteria for this literature review were data from Egypt or Ireland for patients aged 18 years and over with HF concerning the following: (i) clinical characteristics of HF patients, (ii) physician practice (iii) HF management patterns and their impact, and (iv) HF pharmacotherapy. The review included all quantitative studies that directly or incidentally focused on HF pharmacotherapy in either country. The following types of studies were excluded: clinical, or interventional cardiology, right-sided heart failure, pharmacology studies, clinical trials and mechanical device based studies.

2.4 Heart Failure care in Irish literature

Twelve studies on clinical care in HF, conducted in Ireland, were identified. The published Irish literature reflects a widespread acceptance of the value and importance of the implementation of a disease-management programme (DMP) for HF management. All twelve studies were conducted in DMP settings. The studies investigated HF clinical care in DMP from different angles and levels. Eleven of the twelve studies discussed drug utilisation in HF management. The characteristics of these studies are highlighted in Table 2.1. The prescription rates of HF medications prescribed to patients in these studies are presented in Table 2.2.

2.4.1 Implementation of a Heart Failure disease-management programme as an intervention in Heart Failure clinical care in Ireland

The clinical research group in the Heart Failure Unit, St. Vincent's University Hospital defined the DMP service as a comprehensive approach to care of HF encompassing prevention, treatment and follow-up care, including implementation of guidelines. [120, 128-130] The clinical research group designed the DMP service intervention to include a physician with an interest in HF and an HF-specialist nurse. [130] This structured design of HF care had a threefold aim which was: (i) rational and better utilisation of medications; (ii) identification of potential drug-drug interactions; and (iii) extra-intensive patient counselling and education programme. [130]

In a randomised controlled trial, designed to assess the impact of an inpatient and outpatient DMP service on HF-related clinical outcomes in one month and three months after discharge, HF patients with NYHA class IV admitted to the St. Vincent's DMP service were assigned to multidisciplinary care or routine care. [128, 130, 131] Both arms were managed in a cardiology department, received similar guideline-directed medical therapies, including, if indicated the

maximum dose of ACE inhibitors before discharge. The only difference between the two arms was the in-hospital education received by the patients in the multidisciplinary care arm. [129, 130] In the first month post-discharge, no patient died or was rehospitalised within both arms of the study population in which 20% had been admitted to the hospital in the month before enrolment to the study DMP service. [130] At three-month post-discharge, 8% of the multidisciplinary arm of patients had at least one HF-related event, compared to 26% in the routine care arm of patients, *p-value* < *0.05*. [129] The drug utilisation rates of the HF medications are presented in Table 2.2.

In 2015, the same clinical research group examined the five-year survival rate of ambulatory Irish HF patients enrolled in the DMP service from 2002 to 2012. [132] Compared to the non-HF patients, HF diagnosis significantly increased the mortality risk twofold within five years regardless of the patients' EF level. The study reported that the mean age at HF diagnosis was 80 years and that 65% of the HF population was alive five-years post-diagnosis. The study found that a six-month delay in the diagnosis of HF has been associated with a 23% increase in the risk of subsequent HF-related hospitalisation. [132] The study concluded that the accurate early diagnosis of HF in DMP reduces the patients' exposure to inaccurate therapy, thereby improving survival. However, the study did not find a statistically significant difference in the mortality rates or cause of death between HFrEF and HFpEF patients. [132] This finding may reflect the survival benefit of the early initiation of the guideline-directed medical therapies in HF regardless of the EF.

Table 2.1 Characteristics of Heart Failure studies published in Ireland, N = 12.

Author, publication year	Study design	Setting	Population studied	Intervention	Main Aim	Prescribing data published*
McDonald *et al.* [130] 2001	RCT	Tertiary academic hospital, Dublin†	98 hospitalised HF patients	Multidisciplinary care in a DMP	To assess the effects of this intervention on previously high 1-month readmission	Yes
McDonald *et al.* [129] 2002	RCT	Tertiary academic hospital, Dublin†	98 hospitalised HF patients	Multidisciplinary care in a DMP	To assess the effects of this intervention on 3-month readmission	Yes
Ledwidge *et al.* [128] 2003	RCT	Tertiary academic hospital, Dublin†	98 hospitalised HF patients	Multidisciplinary care in a DMP	To evaluate the cost-benefits of multidisciplinary care in DMP	No
Ledwidge *et al.* [131] 2004	Cohort	Tertiary academic hospital, Dublin†	91 hospitalised HF patients	None	To determines the impact of an in-hospital, DMP on appropriate pharmacotherapy, polypharmacy and drug interactions.	Yes
Phelan *et al*. [133] 2009	Cohort	Tertiary academic hospital, Dublin†	39 hospitalised HF patients	None	To determine the proportion of preventable readmissions in DMP	Yes
Mockler *et al.* [134] 2009	Cohort	Tertiary academic hospital, Dublin†	183 HFrEF ambulatory patients	None	To determine the extent, causes, and clinical impact of non-persistence over three years in DMP	Yes

Table 2.1 Characteristics of Heart Failure studies published in Ireland, N = 12, *Cont'd*.

Author, publication year	Study design	Setting	Population studied	Intervention	Main Aim	Prescribing data published*
Bermingham *et al*. [135] 2011	Cohort	Tertiary academic hospital, Dublin†	1,294 ambulatory and hospitalised HF patients	None	To examine the relationship between Beta-2 agonists use and mortality in HF in DMP	Yes
Bermingham *et al*. [112] 2014	Cohort	Tertiary academic hospital, Dublin†	350 ambulatory HF patients	None	To develop a consensus Potentially Inappropriate Medicines in Heart Failure list	Yes
Bermingham *et al.* [136] 2014	Cohort	Tertiary academic hospital, Dublin†	1,476 ambulatory HF patients	None	To evaluate the association of low-dose aspirin with mortality and morbidity risk in HF in DMP	Yes
Moran *et al.* [137] 2014	Cohort	Multi-centre, Ireland	549 ambulatory HF patients	None	To assess the achievement of the target heart rate	Yes
James *et al*. [132] 2015	Cohort	Tertiary academic hospital, Dublin†	733 ambulatory HF patients	None	To assess the 5-year survival of HF patients in DMP	Yes
Murphy *et al*. [138] 2017	Cohort	Tertiary academic hospital, Dublin†	1,292 ambulatory HF patients	None	To assess HFrEF vs HFpEF clinical workload and cost in the first year following hospitalisation in DMP	Yes

† refers to the Heart Failure Unit, St. Vincent's University Hospital, Dublin, Ireland. * prescription rates of the medications from these studies are presented in Table 2.2. **Abbreviations:** DMP, disease-management programme; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RCT, randomised clinical trial.

Table 2.2 Prescription rates of Heart Failure medications in the Irish literature, N = 11.

Study	Renin-angiotensin system inhibitor (%)	Beta-blocker (%)	Mineralocorticoid receptor antagonist (%)	Digoxin (%)	Diuretics (%)
McDonald *et al.* [130] 2001	71	N/A	N/A	59	100
McDonald *et al.* [129] 2002	67	N/A	N/A	49	65
Ledwidge *et al.* [131] 2004	95	N/A	N/A	74	100
Phelan *et al.* [133] 2009	74	69	28	N/A	69
Mockler *et al.* [134] 2009	97	72	15	N/A	90
Bermingham *et al.* [135] 2011	90	63	13	32	85
Bermingham *et al.* [112] 2014	92	87	17	22	78
Bermingham *et al.* [136] 2014	84	84	27	44	93
Moran *et al.* [137] 2014	96	89	45	3	76
James *et al.* [132] 2015	79	65	8	N/A	89
Murphy *et al.* [138] 2017	74	68	9	N/A	92

Data presented as a percentage. **Abbreviations:** N/A, not applicable or not reported.

2.4.2 Reasons for rehospitalisation in Heart Failure

In 2007, Phelan and colleagues investigated the reasons causing rehospitalisation in the St. Vincent's DMP within one-year post-discharge. [133] Despite the structured care of the DMP, the study showed that nearly one-third of hospital admissions could have been prevented. Of these preventable admissions, 20% were caused by drug therapy problems. As the study investigated 39 hospitalisations only, its small sample size impeded the generalisability of its results. [133]

In the same DMP, Mockler *et al.* studied the relationship between HF patient's non-persistence to the HF guideline-directed medical therapies and the clinical outcomes. [134] The medication non-persistence was defined as the discontinuation of an HF guideline-directed medical therapy for any period within a mean follow-up of three years. The study included 183 HF patients, where 30% of patients were categorised as non-persistent. [134] The study found that 50% of non-persistence occurrences did not have a clear documented explanation despite enrolment in DMP. [134] Mockler found that patient's non-persistence to the medications represented a significant predictor of all-cause readmission (Hazard Ratio 3.2, 95% CI 1.74 – 11.34). Compared to the persistent patients, the study found a higher rate of unscheduled clinic visits among the non-persistent patients (1.5 ± 2.7 versus 4.3 ± 5.8 per patient, $p\text{-}value < 0.01$). The author added that the DMP structured care explains the delay of the first occurrence of non-persistence for more than one-year post-discharge. [134] In this study, the clinical factors associated with non-persistence were previous HF-related hospitalisation (odds ratio [OR] 0.314, 95% CI 0.138 – 0.718), chronic kidney disease (OR 1.019, 95% CI 1.0008 – 1.030), and HFrEF (OR 0.961, 95% CI 0.935 – 0.988). However, non-persistence was not associated with polypharmacy. [134]

2.4.3 Achievement of the guideline-recommended therapeutic goals

Moran *et al.* assessed the achievement of the target HR, defined as ≤ 70 bpm, in 549 patients attending 12 HF DMPs throughout Ireland. [137] The study showed that nationally, two-thirds of patients achieved the target HR. Compared to patients within the guideline-recommended target of HR, patients above the target were more likely to be diabetic and in NYHA class III but less likely to be prescribed a beta-blocker. [137] The study investigated the frequency of prescribing the guideline-recommended target dose of the HF medications that affect HR, such as beta-blockers or ivabradine. Beta-blockers were prescribed to 89% of patients and ivabradine to 11% whereas the achievement of the recommended target dose of either medication was moderate as beta-blockers (25%) and ivabradine (10%) only received the target dose. [137] The study found that respiratory disorders were the main barriers to the utilisation and uptitration of the beta-blockers. [137]

2.4.4 Therapeutic complexity in Heart Failure management

The Irish literature investigated two prescribing issues in HF practice in DMP, which were the safety of beta-2 agonists and aspirin use in HF patients. Bermingham and colleagues longitudinally discussed these two issues over twelve-year (1998 – 2010) data of prescribing towards the Irish HF patients in the St. Vincent's DMP. [135, 136]

Bermingham *et al.* did not find any harmful association between beta-2 agonists and the long-term mortality among a study population of 1,294 HF patients. [135] In 2014, Bermingham *et*

al. showed the long-term survival benefit of using low dose aspirin in HF patients in a study population of 1,476 ambulatory HF patients. [136]

Over the twelve years, loop diuretic was the most frequently prescribed medications as to 95% of St. Vincent's DMP patients. [136] ACE inhibitors were prescribed to 85%, beta-blockers to 85% and MRA to 27%. [136] Digoxin was prescribed to 44%. [136] However, it is crucial to consider the time factor and the significant changes in HF prescribing perspectives over this time interval prior to judge the quality of prescription. [1, 139]

2.4.5 Potentially inappropriate prescribing in Heart Failure

In 2004, Ledwidge *et al.* published the effect of the St. Vincent's DMP service on HF prescribing quality on admission and at discharge from an emergency HF admission. [131] In this paper, potentially inappropriate prescribing was defined as (i) a prescription of medications that were contraindicated to the HF guideline-directed medical therapies; (ii) an omission of any of the guideline-directed medical therapies; or (iii) inappropriate dosing of any of the guideline-directed medical therapies as defined according to the ESC guidelines at that time. [131] Pre-admission, patients were prescribed were 66 contraindicated medications, 107 medications' omissions, and 37 inappropriate dose regimens. At discharge from the DMP, these numbers significantly decreased to 31, 33, and 19, respectively, *all p-value* < 0.05 for the comparison between admission and discharge medicines. However, polypharmacy and potential drug-drug interactions had significantly increased by 33% and 62% upon discharge in comparison to the admission results. The study authors explained these results by the fact that the patients were selected following an emergency HF admission implying the disease

severity and the greater need of polypharmacy, in comparison to a more stable ambulatory HF population. [131]

In 2014, the same clinical research group described a different approach to address inappropriate prescribing in HF patients. [112] The study developed the first HF-specific criteria for the potentially inappropriate prescribing, the St. Vincent's PIMHF tool (Appendix 1). This tool consisted of 11 medications or medication classes that are harmful or contraindicated in HF. The application of this tool on ambulatory HF patients enrolled in a DMP found that 15% were prescribed at least one PIMHF agent. Of the list, the non-dihydropyridine CCB were the most frequently prescribed PIMHF item among the DMP patients. [112] Compared to patients who have not been prescribed a PIMHF item, the total number of medications and the comorbidity index were significantly higher, and the prescription of beta-blockers was significantly lower in the patients prescribed a PIMHF. Patients who were prescribed at least one PIMHF agent were at 88% higher risk of combined hospitalisation or mortality over a mean follow-up period of two years. [112]

2.4.6 Economic evaluation of the Heart Failure disease management programme

The implementation of DMP service might raise questions about its economic viability because it may involve employing extra staff members, potentially require higher workload and lengthen the hospital stay.

Data from the St. Vincent's University Hospital have shown the cost-effectiveness of the DMP-based multidisciplinary care, demonstrating significant cost savings from the perspective of the

healthcare provider. [140] The results found a net saving of €37,216 in the arm of the multidisciplinary care over a follow-up period of three months. The costs of hospitalisations in the multidisciplinary care and the routine care arms of DMP in St. Vincent's University Hospital were as follows: €4,114 versus €47,190, *p-value* < *0.05*. The medications represented 3.5% of all-direct hospitalisation costs. [140]

In a study published in 2017, Murphy *et al.* performed a microeconomic comparison between HFrEF and HFpEF patients enrolled in St. Vincent's DMP in terms of the workload and cost. [138] This retrospective analysis included 1,292 patients who were followed up for one year after their admission with HF and enrolment in the DMP. The analysis found the higher costs of HFpEF at the end of the follow-up period due to the non-cardiovascular hospitalisations. [138] The total annual costs of HFrEF and HFpEF were €13,011 and €12,206 per patient in the first year post-discharge. The study found that medication dose optimisation was the major contributor to the workload within the initial months post-discharge regardless of the HF type. Among discharges, diuretics were prescribed to 92% of patients, RASi to 73.7%, beta-blockers to 67.7% and MRA to 8.8%. [138] Compared to HFpEF, adjustment of RASi and beta-blockers doses was more common in the HFrEF cohort within the first three months post-discharge. In HFrEF, the medications related issues represented 4.5% of the total costs of patient care per year. In HFpEF, the medications issues represented 4.3% of the total expenditure per year. [138]

2.5 Heart Failure care in Egyptian literature

The study of HF clinical care in Egypt is very scarce, as only six studies addressed HF care in the Egyptian context. The characteristics of the six studies are outlined in Table 2.3. Of the six studies, only four studies were concerned with HF pharmacotherapy and medications' prescription rates. The prescription rates of HF recommended medications in Egyptian settings are presented in Table 2.4.

2.5.1 Heart Failure care in Egypt

The first original Egyptian HF research was published in 2002 by Bassem Ibrahim over 155 patients in the Cardiology Outpatient Clinic of the National Heart Institute of Egypt in Cairo. [15] This study aimed to estimate the clinical profile and outcomes of HFrEF and HFpEF among Egyptian ambulatory HF patients. Two-thirds of patients had HFrEF. Over a follow-up period of 1.5 years, the rehospitalisation rate per patient was significantly higher in the HFrEF than in the HFpEF (1.01 vs 0.58 rehospitalisation per patient, *p-value < 0.05)*. However, the difference in the mortality rates was not significant between the two types of HF patients. Diuretics were prescribed to 99% of HFrEF patients, ACE inhibitors to 93%, digoxin to 52% and beta-blockers to 37%. [15]

The second Egyptian HF study was conducted in a single private hospital in the governorate of '6th October' and published in 2009. [141] It focused on the clinical presentation and outcomes of acute decompensated HF in 107 hospitalised HFrEF patients. The rehospitalisation rate was 20% in a two-year follow-up. The study found that 83% of patients were NYHA class IV at

admission, but only 12% were prescribed a combination of RASi and beta-blocker at admission. This study did not provide the prescribing data at discharge. [141]

HF prescribing in Egypt was included in a systematic review by Callender *et al.* of *"Heart Failure Care in Low- and Middle-Income Countries"*. [18] The review illustrated a comparison of HF clinical care in non-acute settings between three Middle-Eastern nations, which were Egypt, Tunisia and Lebanon. The review showed that diuretics were prescribed to 82.3% of the Egyptian HF patients while in Lebanon and Tunisia, diuretics were prescribed to 98.3% and 88.7%, respectively. In comparison to Egypt's neighbouring countries, the review showed considerable underutilisation of ACE inhibitors (44%) in Egypt whereas ACE inhibitors were prescribed to 58% of patients in Lebanon and 57% in Tunisia. The review found comparable utilisation rates of beta-blocker (63%) in Egypt, Lebanon (72%) and Tunisia (42%) as well as comparable use of MRAs in Egypt (24.3%), Lebanon (36%) and Tunisia (24%). [18]

Table 2.3 Characteristics of Heart Failure studies published in Egypt, N = 6.

Author, publication year	Study design	Setting	Population studied	Intervention	Main Aim	Prescribing data published*
Ibrahim *et al.* [15] 2002	Cohort	Tertiary academic hospital, Cairo	155 ambulatory HF patients	None	To study the relative contribution of HFrEF and HFpEF in Egyptians	Yes
Hozayen *et al.* [141] 2009	Cohort	Secondary private hospital, 6th October	107 hospitalised HF patients	None	Characteristics and outcome of acute HF patients in Egypt.	No
Samir *et al.* [142] 2011	Survey	Secondary governmental hospital, Alexandria	120 ambulatory HF patients	None	To describe HF patients' abilities to manage their disease.	No
Callender *et al.* [18] 2014	SR-MA	Non-acute settings	N/A	None	To review both published and unpublished information on the presentation, causes, management, and outcomes of HF in LMICs.	Yes
Hassanein *et al.* [16] 2015	Registry	Multi-centre, Egypt	2,145 ambulatory and hospitalised HF patients	None	To describe the clinical characteristics and management of HF patients	Yes
Hassanein *et al.* [143] 2018	Registry	Multi-centre, Egypt	1,634 hospitalised HF patients	None	To evaluate gender differences in the Egyptian cohort of patients hospitalised for acute HF	Yes

*prescription rates of the medications are presented in Table 2.4. **Abbreviations:** HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LMIC, low – medium income countries; N/A, not applicable or not reported; SR - MA, systematic review and meta-analysis.

Table 2.4 Prescription rates of Heart Failure medications in Egypt, N = 4.

Study	Renin-angiotensin system inhibitor (%)	Beta-blocker (%)	Mineralocorticoid receptor antagonist (%)	Digoxin (%)	Diuretics (%)
Ibrahim *et al.* [15] 2002	89	41	N/A	38	97
Callender *et al.* [18] 2014 *	44	62	24	N/A	82
Hassanein *et al.* [16] 2015	87	66	74	41	89
Hassanein *et al.* [143] 2018	83	61	67	37	78

Data presented as a percentage. **Abbreviations:** N/A, not applicable or not reported.

**The source of Egyptian data used in the Callender et al. systematic review was I-PREFER study, a multiregional, cross-sectional, observational study conducted in Latin America, the Middle East, and North Africa. [18, 91] The source and site of the Egyptian data collected for the I-PREFER study were not provided in the study supplementary material.*

2.5.2 The Long-Term Heart Failure Registry of Egypt

As part of the ESC-HF Long-Term Registry, the Egyptian registry included 20 cardiology centres covering the different Egyptian governorates except for the Sinai Peninsula. [16]

The first published study of the registry included an HF population of 2,145 patients. [16] This study is the largest study of HF profile in Egypt in terms of sample size and multicentre design. The study had a different aim than the above three studies as it aimed to highlight the differences of the clinical profiles of hospitalised HF and chronic HF in Egypt and to compare the Egyptian data to the international data in the ESC-HF Long-Term Registry. [16]

The study found that the onset of HF in Egypt occurs 12 years earlier than in Europe (61 years in Egypt versus 73 years in Europe). [16] Also, the prescription rates of HF guideline-directed therapies were significantly lower than the ones of the ESC-HF Long-Term Registry. Among the hospitalised HF patients, diuretics were prescribed to 93%, RASi to 86%, beta-blocker to 66% and MRA to 36%. In ambulatory care, beta-blockers were prescribed to 67% and digoxin to 47% of the HF outpatients. However, the study did not provide an explanation for the low rate of beta-blockers prescription or the high rate of digoxin prescription in this outpatient population. [16]

In 2018, the Long-Term Registry research group published the second output of the registry with a focus on hospitalised HF patients only. [143] The study aimed to examine the effect of gender on the provision of the guideline-directed diagnostic and therapeutic recommendations in Egypt. The results demonstrated a significant difference in the baseline characteristics and the provision of diagnostic and therapeutic interventions to female and male HF patients. For

instance, diuretics prescription rates were significantly higher in the male gender as 81% of males versus 69% of females, *p-value < 0.001*. [143] An MRA was prescribed to 73% of male HF patients and 61% of female patients, *p-value < 0.05*. However, the authors did not investigate the reasons for these gender differences. Also, the authors confirmed that there is a considerable underutilisation of beta-blockers at discharge regardless of the patient's gender. [143] Finally, the registry results showed that the 1-year mortality of HF in Egypt ranges from 26% to 28% post-discharge. [16, 143]

2.5.3 Egyptian Heart Failure patient behaviour

Another aspect of the Egyptian HF literature is the study of patient's behaviour. A survey of 120 patients was carried out by Samir *et al.* [142] in a governmental hospital in Alexandria. The study used an HF self-management survey initially developed in 2000 by Riegel *et al.* [144] to investigate the patient understanding of HF disease progression, treatment evaluation and self-confidence in coping with HF disease complications. [142] The results showed that 66% of this HF population was living a sedentary lifestyle, and 58% were suffering from comorbidities, and 33% had a family history of HF. Although 87% of patient respondents recognised the shortness of breath as a sign for disease progression, only 16% associated ankle oedema with HF and 50% did not consider sudden weight gain as a meaningful HF sign. Only 52% of patients sought medical advice in the case of any new sign or symptoms. [142]

On the level of patients' compliance, 73% only took their HF medications, and 80% took their diuretic therapy, regularly. Regarding patients' compliance to the non-pharmacological measures, 25% only reduced the salt intake, and five per cent decreased their fluid intake. Overall, the survey results identified two crucial factors in relation to patient's medication-

taking behaviour. [142] Firstly, there was a significant positive association between the level of patients' education and treatment administration. Secondly, the study found a significant positive association between the patient's recognition of the sudden changes in symptoms and the administration of treatment. [142]

The Long-Term Registry of Egypt marginally considered a few aspects of the patient's behaviours. For instance, the registry found that patient non-compliance to the medications was the cause of 10% of HF hospitalisation in Egypt. [143] Also, Egyptian HF patients had a higher rate of obesity than HF patients in Europe (47% vs 28%, $p\text{-}value < 0.001$). [143]

2.6 Chronological comparison of Heart Failure management in Ireland and Egypt

Despite the single centred design in the majority of studies, HF literature in Ireland is diverse and covers HF clinical care from different angles. The Irish literature represents a comprehensive study of DMP implementation in terms of clinical and economic aspects as well as the patient's quality of life. In contrast, HF literature in Egypt is still sporadic despite the significant contributions of the Long-Term Registry. Ibrahim's study, published in 2002, was the only reference source for HF information in Egypt for three different international studies published between 2013 and 2015. [13, 18, 145] This may reflect the striking lack of HF data in Egypt before the contribution of the registry. Overall, both countries studied the two types of HF patients that are HFrEF and HFpEF.

Some studies shared factors from which the HF profile and management in Ireland and Egypt can be compared. For a better and accurate study of HF care in the Irish and Egyptian context,

the comparison should be carried out in two timeframes; early and late 2000s. An Egyptian study published in 2002 and an Irish study published in 2004 can lead to a brief comparison about HF profile in Ireland and Egypt at that time (Table 2.5). [15, 131] Interestingly, the largest two HF reports were published more recently in Ireland in 2014 and Egypt in 2015. [16, 137] This allowed conducting an updated comparison of HF management in both countries (Table 2.6). [16, 137]

In the early 2000s, the comparison between Ledwidge *et al.* [131] and Ibrahim *et al.* [15] shows that there was no sizeable difference in the prescription rates of HF medications between the Irish and Egyptian practice except in digoxin prescription (Table 2.5). At that time, digoxin was deemed the first-line therapy for HF management according to the recommendations of the then ESC guidelines. Also, it was considered counter-intuitive to use a negative inotropic agent such as a beta-blocker in patients with impaired systolic function. That is why prescribing of beta-blockers was not reported by Ledwidge *et al.* [131] while it was prescribed to just 37% of the HFrEF study population of Ibrahim *et al.* [15] Notably, both studies mentioned the drug utilisation rates incidentally to the main objectives of the studies. Also, both studies shared a common limitation, which was a small sample size of HF patients recruited from a single centre. This limited the generalisability of the results of the studies.

According to studies published in 2014 and 2015, HF clinical care has not significantly changed (Table 2.6). According to the results of Moran *et al.* [137] and Hassanein *et al.* [16], the utilisation rates of medications in both Ireland and Egypt were comparable. The key differences between the two studies are the high rate of digoxin prescribing and the relatively low rate of beta-blocker prescribing in Egypt. However, both of these studies overlooked some essential ESC

guideline-recommended practices. Firstly, Moran *et al.* included atenolol as an EBBB in HF management despite the existence of DMP structured and specialist care. [137] Secondly, Hassanein *et al.* did not define the type of beta-blockers or diuretics included in the analysis despite being part of the ESC-HF Long-Term Registry. [16]

Table 2.5 Heart Failure management in Ireland and Egypt in the early 2000s.

1st Author	Ledwidge *et al.* [131]	Ibrahim *et al.* [15]
Publication date	2004	2002
Study design	Prospective chart review	Retrospective chart review
Study aim	To determine the impact of an in-hospital, specialist HF care programme on appropriate pharmacotherapy, polypharmacy and drug interactions.	To study the prevalence of HFrEF and HFpEF in an Egyptian population
Clinical setting	DMP Service, St. Vincent's University Hospital, Dublin, Ireland	Cardiology outpatient clinic, National Heart Institute, Cairo, Egypt
Population	91 hospitalised HF patients	155 ambulatory HF patients
HFrEF	68%	66%
Gender (male)	66%	76%
Mean age ± SD (years)	71 ± 10 years	60 ± 10 years
Commonest cause of HF	Ischaemic heart disease (50%)	Ischaemic heart disease (72%)
Valvular diseases	20%	23%
Diabetes	21%	> 33%
Smoking prevalence	37%	23%

Table 2.5 Heart Failure management in Ireland and Egypt in the early 2000s, *Cont'd.*

1st Author	Ledwidge *et al.* [131]	Ibrahim *et al.* [15]
Heart Failure medications' prescription rates among patients having Heart Failure with reduced ejection fraction (HFrEF)		
Number of patients	**62**	**102**
RASi	**95%**	**93%**
Beta-Blocker	**N/A**	**37%**
Digoxin	**74%**	**52%**
Diuretics	**100%**	**99%**

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; N/A, not applicable or not reported in the study; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker); SD, standard deviation.

Table 2.6 Heart Failure management in Ireland and Egypt in 2014 - 2015.

1st Author	Moran *et al.* [137]	Hassanein *et al.* [16]
Study type	Prospective observational study	Prospective observational study
Clinical Setting	Multi-centre (n =12 hospitals)	Multi-centre (n =20 hospitals)
Setting type	Disease management programmes	Cardiology wards
Study aim	To identify the prevalence of patients with heart rate >70 To identify the proportion of patients achieved the target doses of heart rate-controlling medications	To describe HF profile, characteristics and management in Egypt
Population size	549	607
Population type	Chronic stable HF	Chronic stable HF
HFrEF	51%	75%
Gender (male)	71%	64%
Mean age (years)	N/A	57
Commonest aetiological cause of HF	N/A	Ischemic heart disease
Previous hospitalisations	N/A	35%
Diabetes	23%	32%
Smoking prevalence	33%	52%

Table 2.6 Heart Failure management in Ireland and Egypt in 2014 – 2015, *Cont'd*.

1st Author	Moran *et al.* [137]	Hassanein *et al.* [16]
Heart Failure medications' prescription rates		
RASi	97%	90%
Beta-Blockers	90%	67%
MRA	45%	87%
Ivabradine	11%	20%
Digoxin	3%	47%
Diuretics	76%	85%
Achievement of target dose		
Beta-Blockers Target dose achieved	25%	N/A
Ivabradine Target Dose achieved	10%	N/A
Device-based therapy		
CRT/ICD	28%	2%

Abbreviations: CRT, cardiac resynchronisation therapy; DMP, disease management programmes; HF, heart failure; ICD, implantable cardiac defibrillator; MRA, mineralocorticoid receptor antagonists; N/A, not available or not reported in the study; RASi, renin-angiotensin system inhibitor (ACE inhibitor/ angiotensin-II receptor blocker).

2.7 Gaps in knowledge

The present literature review identified two levels of gaps in knowledge: (i) common gaps in knowledge in both countries; and (ii) country-specific gaps in knowledge.

2.7.1 Gaps in knowledge in both Ireland and Egypt

There is considerable research on HF in Ireland and Egypt; however, very little of it is solely concerned with drug utilisation, and none is concerned with guideline-led prescribing. In most cases, prescribing data were presented incidentally to the other research aims. Overall, the data from 2000 to 2018 showed that in Ireland, the range of RASi prescription was 67% - 97% of patients, beta-blockers (63% – 89%) and MRA (8% - 45%) while in Egypt, their ranges were RASi (44% - 89%), beta-blockers (41% - 66%) and MRA (24% - 74%).

All the aforementioned studies overlooked some important prescribing-related factors. Firstly, the appropriate choice of the beta-blockers is crucial in HF care as only the four EBBB are proven to be beneficial in HF management. [1] Secondly, the achievement of the recommended target dose is one of the most important ESC guidelines' recommendations to get full benefits of the prescribed medications. [1, 84] This point was discussed only once in the Irish HF literature [137] but was not studied in the Egyptian literature. Thirdly, the identification and consideration of the evidence-based relative or absolute contraindications are essential for assessing the quality of HF prescribing. [1, 146] Hence, contraindications represent a potential explanation for the omission of the evidence-based medications in many circumstances. Consequently, the exact causes of non-adherence to the guidelines are unknown.

2.7.2 Gaps identified in the Irish Heart Failure literature

Almost all research was performed in Dublin and mainly, in a single tertiary academic care setting. Also, routine clinical practice of HF is not assessed in any of the HF studies. Heart failure DMPs offer structured care; however, this type of care may not be available to all patients nationally. Furthermore, no study focussed on vulnerable populations such as the residents of nursing homes. Finally, the majority of the Irish studies were selective in the patient recruitment process as some studies excluded patients having diseases that adversely affect the survival [128-131] while others excluded patients in whom HF was not the primary reason for hospitalisation. [128-131, 133, 137]

2.7.3 Gaps identified in the Egyptian Heart Failure literature

The review of the Egyptian literature points to many gaps in knowledge. Firstly, all the Egyptian literature covered cardiology departments only and did not include other types of healthcare settings that have the ability to discharge patients to home, such as the critical care medicine departments. Secondly, the prevalence of potentially inappropriate medicines was not addressed in the literature. Thirdly, the Egyptian studies did not discuss any quality measure or intervention in order to improve the prescribing outcomes and particularly, the prescription of beta-blockers and digoxin. Finally, the guideline-recommended target goals of therapy, such as target HR or target BP, were not considered in any of the studies.

3 Chapter 3

A Tool for Assessment of Heart Failure Prescribing Quality: A Systematic Review and Meta-Analysis

The previous two chapters discussed HF pharmacological management worldwide and particularly, in Ireland and Egypt. This chapter aims to identify the potential quantitative tools assessing HF guideline-led prescribing objectively and overcoming the problems of sole use of prescription rates. Evidence from this chapter will be used in the following chapters to assess guideline-led prescribing in various settings.

The work of this chapter has been published as: El Hadidi S, Darweesh E, Byrne S, Bermingham M. A tool for assessment of heart failure prescribing quality: A systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety 2018;27(7):685-94.[147]

3.1 Abstract

3.1.1 Introduction

Heart Failure guidelines aim to standardise patient care. Internationally, prescribing practice in HF may deviate from guidelines, and so a standardised tool is required to assess prescribing quality.

3.1.2 Aims

A systematic review and meta-analysis were performed to identify a quantitative tool for measuring adherence to HF guidelines and its clinical implications.

3.1.3 Methods

Twelve electronic databases were searched to include studies reporting a comprehensive tool for measuring adherence to prescribing guidelines in HF patients aged ≥ 18 years. Qualitative studies or studies measuring prescription rates alone were excluded. Study quality was assessed using the Good ReseArch for Comparative Effectiveness (GRACE) Checklist for rating the quality of observational studies of comparative effectiveness.

3.1.4 Results

In total, 2,455 studies were identified. Sixteen eligible full-text articles were included (n =14,354 patients, mean ± standard deviation (SD) age 69 ± 8 years). The Guideline Adherence Index (GAI-3), and its modified versions were the most frequently cited tool (n = 13). Other tools identified were: the Individualised Reconciled Evidence Recommendations, the Composite Heart Failure Performance, and the Heart Failure Scale. The meta-analysis included the GAI studies of good-high quality. The average GAI-3 was 62%. Compared to Low-GAI,

High-GAI patients had a lower mortality rate (7.6% vs 33.9%) and lower rehospitalisation rates (23.5% vs 24.5%); *both p-value* < 0.05. High-GAI was associated with reduced risk of mortality (Hazard Ratio 0.29, 95% CI 0.06 - 0.51) and rehospitalisation (Hazard Ratio 0.64, 95% CI 0.41 - 1.00). No tool was used to improve prescribing quality.

3.1.5 Conclusion

The GAI is the most frequently used tool to assess guideline adherence in HF. High-GAI is associated with improved HF outcomes.

3.2 Introduction

Landmark clinical trials demonstrated the significant benefits of guideline-directed medical therapies on mortality, hospitalisation and patient's quality of life in HF. [55, 148, 149] However, international reports suggest that prescribers do not optimally adhere to the recommendations of HF practice guidelines. [150-152] It has been shown that under-prescribing of guideline-directed medical therapies is associated with worsening HF and higher rates of HF hospital admissions and mortality. [79, 134, 153] Furthermore, where these agents are prescribed, but at lower than the target dose, patients may not obtain the full beneficial effect of the agents. [151, 154] Thus, HF clinical care could be vastly improved with the optimal use of guideline-directed medical therapies. [1, 154]

Guideline adherence refers to the adoption of clinical practice guidelines by clinicians in their routine clinical practice, rather than to the patients' adherence. There remains a wide variation in HF prescribing patterns, and quality internationally [13, 151, 155] and several barriers to guideline adherence have been described. Prescribing for patients with multiple comorbidities [151], polypharmacy [156], or advanced age [156] can affect prescriber's adherence to guidelines. Furthermore, the lack of resources in the healthcare setting or lack of knowledge on behalf of the prescriber may also play a role in poor guideline adherence. [157]

Given the complexity of HF management, the simple prescription rates alone are not sufficient to evaluate prescribing quality as they do not consider factors such as a patient's eligibility for or contraindication to therapy or achievement of the target dose. Some health systems have developed HF performance measures, which include prescribing indicators. However, these measures often involve a simple assessment of a single prescription item and are not comprehensive regarding the complex HF practice guidelines. [158, 159] The Guideline

Adherence Index (GAI) addresses many of these shortcomings and has been widely cited since its first publication in 2005 [46] and other comprehensive tools may have been developed. [160, 161]

3.2.1 Aims

This systematic review and meta-analysis were performed in order to identify and characterise the objective tools for quantifying adherence to guideline-led prescribing in HF practice and to assess the clinical outcomes associated with physician's guideline adherence measured by such tools.

3.3 Methods

3.3.1 Review protocol

Prior to the start of the review process, a protocol for the work was submitted as part completion of PG7016 Systematic Reviews for the Health Sciences, a postgraduate training module in University College Cork. The protocol was reviewed by Professor John Browne, School of Epidemiology and Public Health, University College Cork. This systematic review and meta-analysis were performed in line with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. [162]

3.3.2 Study eligibility criteria

The inclusion criteria for the systematic review were studies: (i) specific to chronic or acute HF patients aged ≥ 18 years; (ii) measuring adherence to a national or international chronic or acute HF guideline; and (iii) using a quantitative review tool to assess adherence to practice guidelines. The exclusion criteria for the systematic review were: (i) studies reporting prescription rates in absence of a quantitative or comprehensive prescribing review tool; and (ii) qualitative studies.

3.3.3 Search methods

3.3.3.1 Information sources

The following electronic databases were searched in April 2016: Medline PubMed, Scopus, Web of Knowledge, Science Direct, EBSCO (Academic search complete, CINAHL, and PsycINFO), EMBASE, Cochrane Library, Campbell Collaboration, Open Grey and Grey Lit. No restriction was placed on publication date or language.

3.3.3.2 Search terms

The following search terms were combined as appropriate across each database: heart failure, care indicator, global prescribing score, guideline adherence indicator, guideline adherence index, GAI, guideline compliance, guideline implementation, implementation of guidelines, process indicator, quality circle, and strategies for guideline implementation, (Appendix 2). The search terms were used as single terms or combined via Boolean logic (AND, OR) in each database.

3.3.4 Study selection

A database search was performed, and duplicate results were removed. Two reviewers (SE, MB) independently reviewed the titles and abstracts of studies identified in the search. Studies that were eligible for full-text review were identified and reviewed by the two reviewers for final determination of study inclusion in the systematic review and meta-analysis.

3.3.5 Assessment of risk of bias in included studies

Risk of bias assessment was performed using the Good ReseArch for Comparative Effectiveness (GRACE) Checklist for observational studies. [163]

3.3.6 Outcomes

A meta-analysis was performed on studies identified in the systematic review that used the Guideline Adherence Index (GAI) tool. Studies of good to high quality according to the GRACE Checklist were included in the meta-analysis. Overall GAI is a mean score of the guideline adherence levels (range from 0% - 100%) of all the eligible patients prescribed HF

medications as recommended by the relevant guidelines. The GAI-3 is the proportion of the three principle HF guideline-directed medical therapies: RASi, beta-blocker and MRA that is actually prescribed to each patient according to the indications of the relevant guidelines. In this study, GAI scores are categorised into (i) High-GAI that is prescription of ≥ 2 recommended HF agents and (ii) Low-GAI that is prescription of < 2 recommended HF agents. The GAI can also be calculated for each pharmacological class individually as the proportion of eligible patients prescribed the pharmacological class. This is compared to the percentage of patients prescribed a medication out of the total population regardless of the patient's eligibility.

3.3.7 Statistical analysis

Data were extracted from the studies identified using a structured form in Microsoft Office Excel® 2016. Pooled odds ratios (OR) and respective 95% confidence intervals (CI) were displayed using the forest plot generator of DistillerSR®. Hazard ratios and 95% CIs were pooled using NCSS® Statistical Software for Data Analysis v.11 for meta-analysis of Hazard Ratios, computed by random-effects regression for combining study data. Cochran's Q test was used to estimate heterogeneity. Random effects were applied to compensate for the potential for between-study heterogeneity in observational studies. Means were rarely reported with an estimate of variability and consequently, are presented as pooled mean with its appropriate SD or the range of means.

3.4 Results

3.4.1 Search results

A total of 2,454 titles were identified through the database search and one manuscript via hand search (Appendix 2). Of these, 1,529 were duplicates. Following title and abstract review, 66 studies were identified as eligible for full-text review. Finally, 16 studies were considered relevant to this systematic review, as shown in the PRISMA flowchart (Figure 3.1).

3.4.2 Profile of included studies

The characteristics of each included study are shown in Table 3.1. All included studies were non-interventional. Study populations ranged from 58 – 3,292 HF patients. The combined study population included in the review was 14,354 HF patients, and the mean ± SD age was 69.0 ± 8.0 years. Patients having HFrEF were included in all 16 studies [46, 161, 164-177] and patients having HFpEF in 11 studies. [46, 161, 164, 167, 169-171, 175, 176, 178, 179]

The studies reported the use of prescribing review tools in several different healthcare settings including eight studies performed in ambulatory care [46, 166-169, 172, 176, 178], six studies in primary care [164, 168, 170, 173, 175, 180] and seven studies in hospital inpatient settings [161, 166, 171-173, 176, 179]. Seven studies [46, 166-168, 172, 178, 179] included a follow-up period of 6-12 months, while two studies [161, 176] reported a follow-up period of almost two years.

Twelve studies were performed in Europe, six of which were performed in Germany [46, 164, 172, 176, 178, 180]. All studies assessed guideline adherence by reference to ESC guidelines except Popescu *et al.* [161], which used an American quality measure. Fifteen studies were adjudged to

be of good - high quality (Table 3.1). One study was judged to be of poor quality and was not included in the meta-analysis. [166]

3.4.3 Tools identified in the systematic review

Four objective tools were identified in this review: i) the GAI [46]; ii) the Composite Heart Failure Performance [161]; iii) the Heart Failure Scale [170] and iv) the Individualized Recommended Evidence-based Reconciliation (IRER) [169].

The GAI was initially defined by Komajda and colleagues as the proportion of the indicated guideline-directed medical therapies prescribed for every patient by their physicians according to the recommendations outlined in the ESC 2001 guidelines. [46] Thirteen of the 16 studies identified used the GAI. [46, 164, 166-168, 171-173, 175, 176, 178-180] This tool has been modified in several ways since its publication, and only two studies used the original tool. [168, 175] Modifications to the GAI include the consideration of contraindications to therapy [167, 171-173, 175, 176, 180], recommended target doses [167, 180], general practitioner rationale [164, 173] and patients' socioeconomic level [171, 173] as eligibility criteria for guideline adherence. While 11 studies reported GAI for both HFrEF and HFpEF patients, only one study reported the GAI results for each HF type [176].

Each of the other guideline adherence tools identified has been reported in a single study. The Composite Heart Failure Performance is calculated as a ratio of the number of HF patients in a given hospital who received guideline-directed medical therapy divided by the number of HF patients in that hospital who should have received the indicated treatment. [161] Therefore, this tool was developed for application at a hospital population level rather than at a direct patient level.

The third tool identified is the Heart Failure Scale. [170] It is calculated as the percentage of HF patients appropriately receiving the following elements of care: laboratory tests, lipid profile, prescription of a RASi and prescription of a beta-blocker. [170] The fourth tool is the IRER. [169] This tool consists of software that merges the guidelines of several chronic diseases and includes recommendations on vaccination, lifestyle measures and therapy goals as well as pharmacological therapy. The software generates a list of evidence-based recommendations personalised to each HF patient. [169] This is the most recently published tool and is characterised by its multi-disciplinary approach; however, it does not take contraindications to therapy into consideration. [169] All non-GAI studies took into account some clinical aspects of prescribing, such as availability of echocardiography results or serum creatinine level as a pre-requisite to RASi prescription. The components of clinical care considered by each tool are described in Table 3.2.

No tool identified here has been utilised as a tool to improve or optimise the quality of prescribing in HF patients. Furthermore, no tool assessed the management of acute HF.

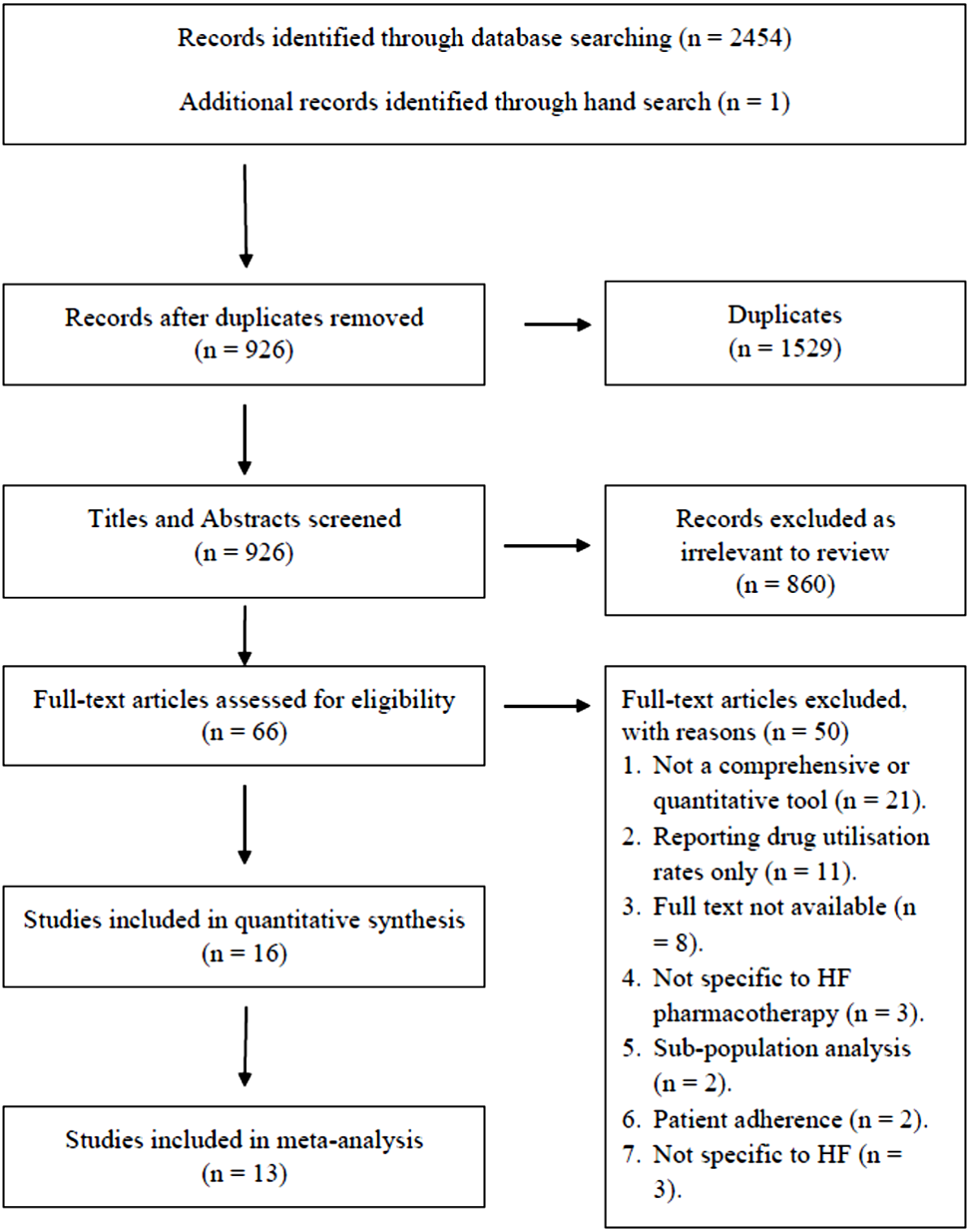


Figure 3.1 Flow diagram of the systematic review search strategy.

3.4.4 Measured guideline adherence and changes in guideline adherence indices over time

The studies reporting the IRER and the Composite Heart Failure Performance both reported guideline adherence of > 90% whereas the Heart Failure Scale reported a relatively low guideline adherence score of 1.6 / 4. Among studies reporting GAI, the mean GAI-3 was 62.9% ± 20.4% (range 14% - 95%) in the period from 2005 to 2016. These changes reflect the on-going modifications to the GAI-3 and guidelines updates. Also, the small sample size may adversely affect overall GAI-3 score in certain studies such as Oliveira *et al*. [171]

3.4.5 Guideline adherence tools compared to the prescription rates

Four GAI based studies reported a comparison between the simple prescription rates and the GAI scores for RASi, beta-blocker and MRA (Table 3.3). In each pharmacological class, the GAI is calculated as the proportion of eligible patients whose physicians prescribed according to the guidelines. Two studies [46, 171] showed that GAI scores of pharmacological classes were higher than the prescription rates as GAI considered the patient's eligibility to therapy as the denominator. However, the other two studies [175, 180] showed the opposite result. This paradox was explained by Klimm *et al.* [180], that the GAI score should take into account both contraindications and achievement of target dose in order to reflect the guideline's recommendations comprehensively. However, in Bosch *et al.* [175], the higher prescription rates were justified as HF medications were prescribed to patients in absence of their guideline-outlined indications.

3.4.6 Daily target dose prescription

Six studies [164, 167, 173, 175, 179, 180] reported the frequency of HF patients receiving ≥ 50% of the daily target dose of the guideline-directed medical therapies (Figure 3.2). Overall, 57% of patients were prescribed ≥ 50% of the target dose of RASi and 33.2% of patients were prescribed ≥ 50% of the target dose of beta-blocker. The daily dose of MRAs was studied in two populations [173, 179], where ≥ 50% daily target dose was prescribed to 95.6% and 100% of patients respectively.

3.4.7 Guideline adherence achieved by cardiologists and general practitioners

Three studies compared the general practitioner (GP) and cardiologist prescribing patterns. Stork *et al*. calculated the GAI-3 as 67% for cardiologists and 60% for GPs *(p-value = 0.01)*. [176] Luttick *et al*. calculated the GAI-3 for each type of prescriber at baseline and one-year follow-up. [168] The GAI-3 rates for GP prescribers were 95% at baseline, and 92% at follow-up and the GAI-3 rates for cardiologists were 94.5% at baseline and 91% at follow-up. However, the difference at both time points was non-significant. [168] Elsewhere, Bosch *et al.* [175] found that the percentage of patients receiving the guideline-directed target dose of ACE inhibitors was significantly higher when prescribed by a cardiologist than when prescribed by a GP (29.5% vs 14.3%, *p-value < 0.05*). Elsewhere, Visca and colleagues found that single or team-based GP practice has no relationship with the HF composite score. [170]

3.4.8 Achievement of High Guideline Adherence Index

High-GAI achievement was calculated in eight GAI studies [46, 164, 167, 172, 176, 178-180]. The mean number of patients achieving High-GAI was 53.8 ± 12.2% (range 38% [176] to 71% [172, 179]).

Before 2010, the mean proportion of HF patients achieving High-GAI was 42.5% while in the period since 2010, a mean of 63% of patients have achieved High-GAI. Clinical factors associated with High-GAI achievement are illustrated in Figure 3.3.

3.4.9 Barriers to achieving guideline adherence

Twelve studies identified barriers to guideline adherence in their study population. Seven studies cited increasing patient age of HF patients [165, 168, 172, 174-177] and five studies cited patient comorbidity burden. [164, 165, 167, 175, 176] Other barriers to guideline adherence identified were: increasing NYHA class [172, 175] and the presence of obstructive lung disease [177], chronic kidney disease [165, 173, 177], hypotension [164, 165, 171] and bradycardia [164, 171, 177]. However, two studies reported that there was no explanation available for guideline non-adherence in up to 15% of patients in their populations [165, 173].

3.4.10 Clinical outcomes associated with Guideline Adherence Index

The clinical impact of guideline adherence was studied in seven study populations. [46, 167, 168, 172, 176, 178, 179] Two studies reported Cox proportional hazards models estimating the relationship between the GAI score and one-year mortality. [172, 178] Mortality risk associated with High-GAI ranged from 5% to 13% while mortality risk associated with Low-GAI ranged from 10% to 21.5% (*p-value < 0.005 each*). On the other hand, six studies [46, 167, 171, 176, 178, 179] reported mortality rates as mortality percentage in the whole population sample, High-GAI and Low-GAI cohorts separately as 16.0 ± 8.1%, 7.6 ± 3.0% and 33.9 ± 18.8%, respectively. Both approaches of mortality outcome measurement showed a significant mortality benefit of High-GAI levels over Low-GAI levels. Adjusted for age and sex, High-GAI score was a significant

independent predictor of mortality risk reduction in five studies (overall Hazard Ratio 0.289, 95% CI 0.061 - 0.516, Figure 3.4).

All-cause hospital admission was studied in three populations [46, 167, 168], where the overall mean ± SD rehospitalisation rate was 9.1 ± 6.1%. Also, the variation of rehospitalisation rates among the different GAI cohorts was studied in two study populations [46, 172], where the overall mean ± SD rehospitalisation rate per 100 patients in the High-GAI cohorts was 23.5 ± 20.2% but in the Low-GAI cohorts was 24.23 ± 10.6%. Paradoxically, Zugck *et al.* reported that HF hospitalisation rate was significantly higher in the High-GAI cohort than in the Low-GAI cohort (50% vs 36%, *p-value = 0.026*) although a clear explanation for this effect was not offered. [172] Finally, in the MAHLER study over a 12-month follow-up period, the risk of rehospitalisation was significantly reduced in patients with High-GAI compared to those with Low-GAI (Hazard Ratio 0.64, 95% CI 0.41 - 1.00). [46]

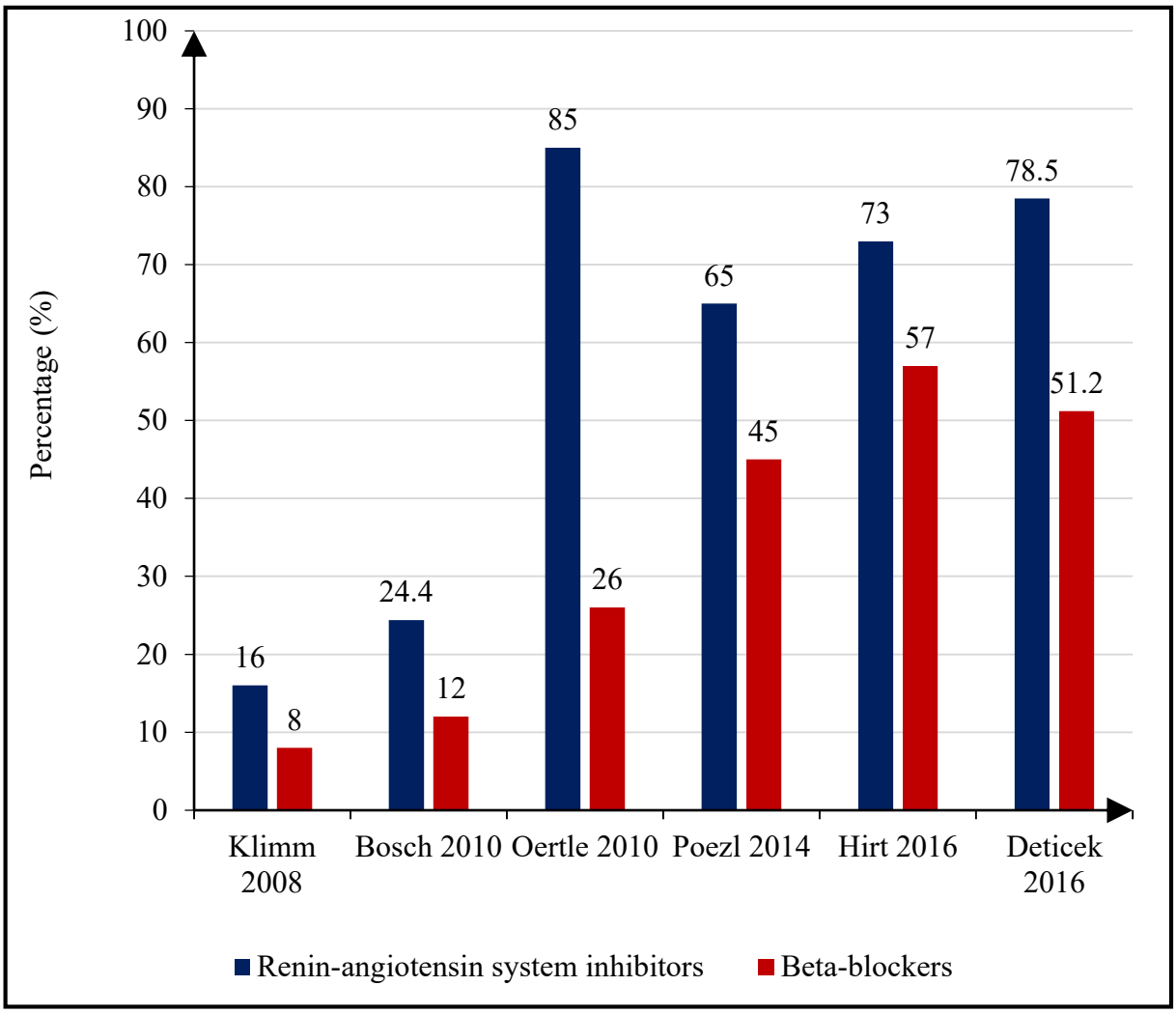


Figure 3.2 Heart Failure patients prescribed ≥ 50% of the recommended target dose of (i) renin-angiotensin system inhibitors (ACE inhibitor or angiotensin-II receptor blocker) and (ii) beta-blockers.

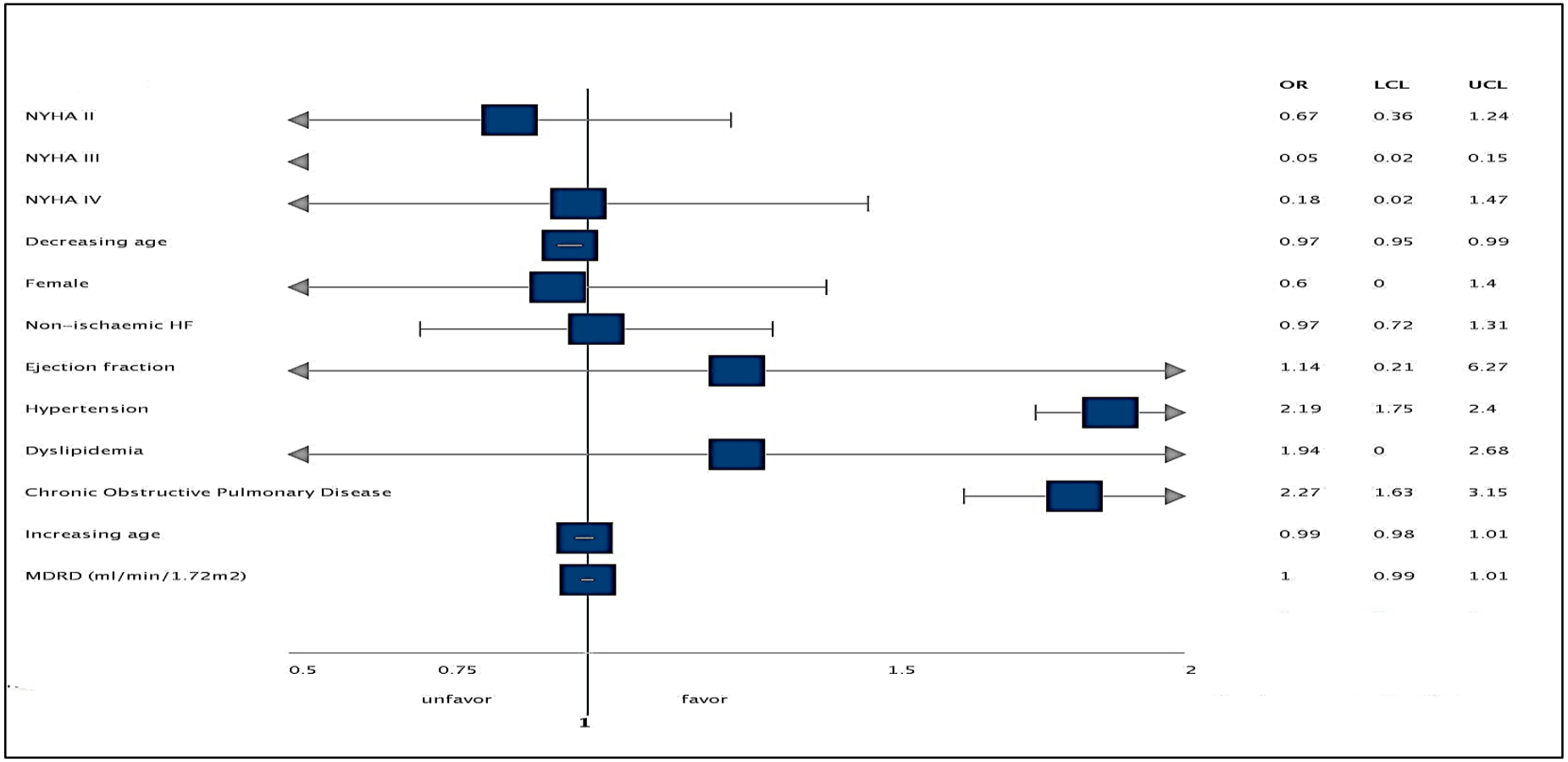


Figure 3.3 Clinical factors associated with High Guideline Adherence Index based on data from two study populations (Bosch [175] and Frankenstein [178]) using multivariable Cox regression analysis model.

Abbreviations: HF, heart failure; LCL, lower confidence level; MDRD, modified diet for renal disease; NYHA, New York Heart Association functional classification; OR, odds ratio; UCL, upper confidence level. Model I^2 static = 73.1%, *p-value* < *0.001*.

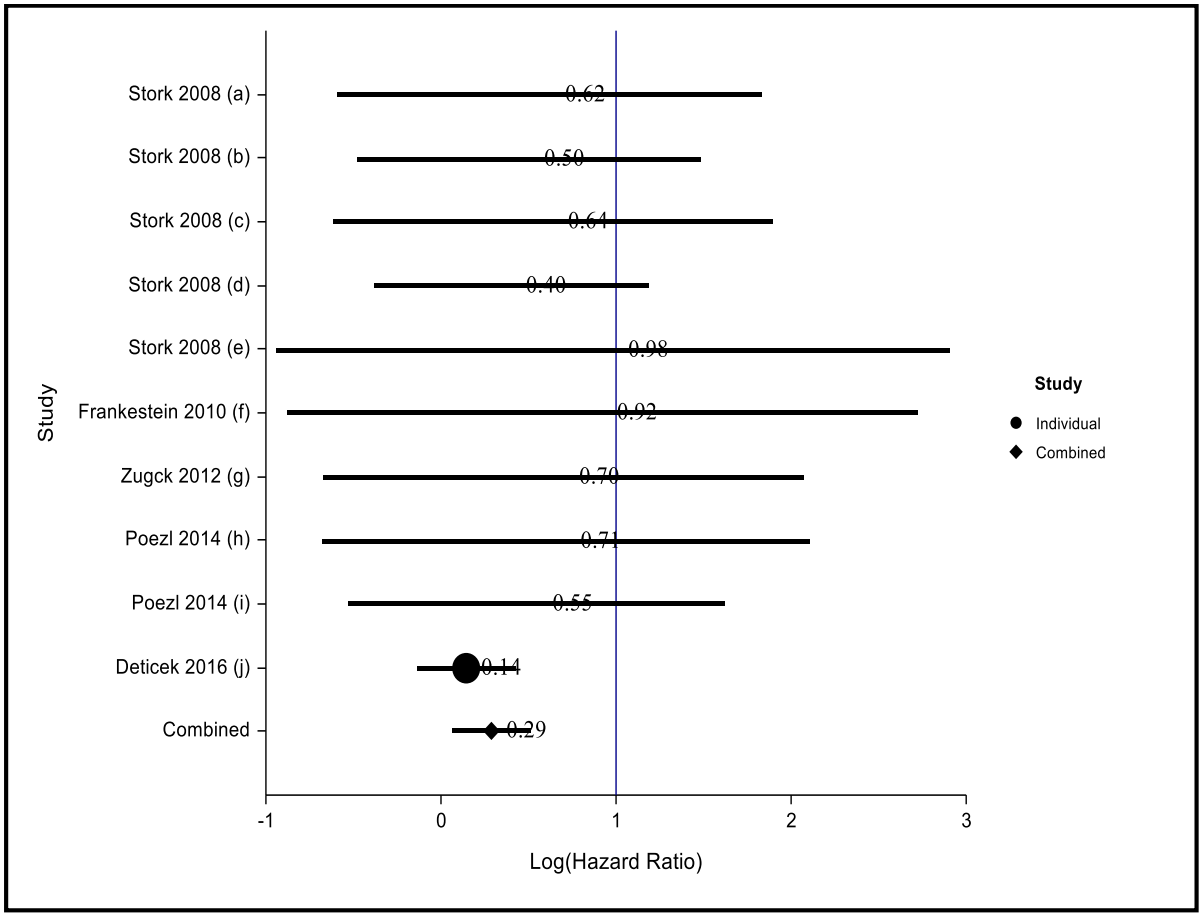


Figure 3.4 A meta-analysis of the association between Guideline Adherence Index and mortality. The following Guideline Adherence Index (GAI) parameters were seen to be associated with mortality risk reduction: (a) GAI-3 Medium compared to GAI-3 poor; (b) GAI-3 High compared to GAI-3 low; (c) GAI-5 Medium compared to GAI-5 poor; (d) GAI-5 High compared to GAI-5 low; (e) high dose of ACE inhibitor/angiotensin-II receptor blocker; (f) GAI per 10% increase; (g) GAI-3; (h) improvement in GAI over one year; (i) improvement in target dose GAI over one year; (j) GAI-123 compared to GAI-0. Results (a) – (e) based on HFrEF cohort, n = 641. **Definitions:** GAI-0, No heart failure recommended medication prescribed; GAI-123, prescription of any one of the top three heart failure recommended agents; GAI-3, prescription of all the top three recommended heart failure medications; GAI-5, prescription of all five heart failure recommended medications. *Cochran's Q = 3.8; p-value = 0.924.*

Table 3.1 Profile and characteristics of the studies included in the systematic review, N = 16.

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Komajda, France, Italy, Netherlands, Spain, Germany, United Kingdom 2005 (46)	Prospective, observational, multicentre study in ambulatory care settings.	Clinical impact of guideline adherence on hospitalisation and time to hospitalisation	1,410	68.6	European Society of Cardiology 2001	GAI	(Medications indicated / Total medications prescribed) x100	GAI-3 = 60% GAI-5 = 63%	Good
Stork, Germany 2008 (176)	Prospective, observational, multicentre study in hospitals and ambulatory care settings.	Determinants of guideline adherence	1,054	72.6	European Society of Cardiology 2001	GAI	Consider contraindications	HFrEF GAI-3 = 67% HFrEF GAI-5 = 75% High HFrEF GAI-5 = 47%	High
Klimm, Germany 2008 (180)	Prospective, observational, multicentre study in primary care units.	Assessment of guideline adherence among general practitioners	167	68.2	German guidelines 2005	GAI	Consider contraindications and target dose	GAI-3 = 25%, mGAI-3 = 16% Target dose RASi = 16% Target dose beta blocker = 8% Perfect GAI = 44%	High
Popescu, USA 2008 (161)	Retrospective, observational, multicentre study in hospitals	Assess hospital compliance with quality measures	N/A	N/A	Centre for Medicare and Medicaid Services performance measures	Composite Heart Failure Performance	(Number of patients prescribed ACE inhibitor / Number of ACE inhibitor candidates) x 100	Performance rate = 90.9%	High

Table 3.1 Profile and characteristics of the studies included in the systematic review, N = 16, *Cont'd*.

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Bosch, Netherlands 2010 [175]	Prospective, observational multicentre study in primary care	Evaluation of heart failure treatment in Dutch primary care	357	76	European Society of Cardiology 2005	GAI	None	GAI-3 = 53.3% RASi target dose = 48.8% Beta blocker target dose = 12% RASi + beta blocker + MRA = 10.4%	High
Frankenstein, Germany 2010 [178]	Prospective, observational, multicentre study in ambulatory care settings	Assessment of impact of guideline adherence on survival	3,292	61	European Society of Cardiology 2005	GAI	Consider contraindications ; relative GAI	Crude GAI = 47.9% (1994- 2000) Crude GAI = 70.8% (2001-2007) Relative GAI-3 improved from 66% (2000) – 100% (2007)	High
Oertle, Switzerland 2010 [173]	Retrospective, observational single-centre study in hospital setting	Understanding the suboptimal utilisation of evidence-based medicine in heart failure	348	82	European Society of Cardiology 2005	GAI	Corrected for chronic kidney disease and adjusted by general practitioners' rational	GAI-3 = 70%, GAI-5 = 60% Corrected GAI-5c = 80% Adjusted GAI-5a = 90%	Good
Zugck, Germany 2012 [172]	Retrospective, observational, multicentre study in various medical settings	Evaluation of guideline adherence level and its determinants	2,682	66	European Society of Cardiology 2005	GAI	Consider contraindications	Perfect GAI = 71.1% Moderate GAI = 22.4% Poor GAI = 6.5%	Good

Table 3.1 Profile and characteristics of the studies included in the systematic review, N = 16, *Cont'd*.

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Visca, Italy 2013 [170]	Retrospective, observational, multicentre in primary care units	Assess impact of team practice in family medicine	1,962,137 admissions	54	New Zealand guidelines 2009 & other international guidelines	Heart Failure Composite Scale	Scale of four evidence-based criteria (Serum creatinine + lipid levels + ACE inhibitor + beta blocker)	Heart Failure Composite Scale = 1.64/4	High
Oliveira, Brazil 2013 [171]	Prospective, observational single-centre hospital	Evaluation of physician guideline adherence	53	57	Brazilian guidelines2009	GAI	Consider contraindications	GAI-3 = 40.7%	Good
Poelzl, Austria 2014 [167]	Multi-centre in ambulatory care settings	Study of guideline adherence and dose effect	2,824	65	European Society of Cardiology 2012	GAI	Consider target dose	GAI = 75.7% Improved target dose based GAI = 64.4%	High
Yoo, Korea 2014 [166]	Retrospective, observational, multicentre study, hospital settings	Guideline adherence assessment and its outcomes	1,319	69	European Society of Cardiology 2008	GAI	None	GAI-0 = 1.5% GAI-3 = 43.6% Good GAI = 82%	Poor
Luttik, Netherlands 2014 [168]	Prospective, observational, multicentre study in primary care units	Assessment of guideline adherence in general practice compared to heart failure clinics	189	73	European Society of Cardiology 2008	GAI	GAI at two time-points	GP GAI baseline = 95% GP GAI1year = 92% HF Clinic GAI baseline = 94.65% HF Clinic GAI1year = 91.1%	High

Table 3.1 Profile and characteristics of the studies included in the systematic review, N = 16, *Cont'd*.

Study author, country, year	Study design	Study aim	Sample number	Mean age (years)	Guideline Assessed	Assessment Tool	Equation / Modifications	Main outcomes of tool	Quality
Ho, Australia 2014 [169]	Retrospective, observational, single centre study, in ambulatory care	Assess guideline adherence in heart failure patients with multiple comorbidities	255	81	Australian guidelines 2009 and 2012	Individual Reconciled Evidence-based Recommendations (IRER)	Reconciled list of evidence-based recommendations individualised specifically for each patient	Full evidence-based prescription = 93.7% Therapeutic goals achieved = 88.7% Lifestyle modifications = 64%	High
Hirt, Germany 2016 [164]	Three-stage study in primary care units	Assessment of guideline adherence in general practice units	206	77	European Society of Cardiology 2012	GAI	Consider contraindications, target dose and prescriber concerns	Contraindication based GAI = 56% Target dose based GAI = 3%	Good
Deticek, Slovenia 2016 [179]	Prospective, single-centre study in a hospital	Assessment of therapy modifications in inpatients	198	77	European Society of Cardiology 2012	GAI	Consider target dose and contraindications	GAI-123 = 90% GAI-3 = 14% mGAI-3 = 7.1% GAI-5 = 2.5%	High

Abbreviations: GAI, Guideline Adherence Index; GAI-5, prescription of RASi ± beta-blocker ± MRA ± cardiac glycoside (digoxin) ± loop diuretic; GAI tertiles, (a) Perfect GAI is prescription of the three principle HF medications; (b) Medium GAI is prescription of two out of the three HF medications; (c) Poor GAI is prescription of one or zero HF medications; mGAI, modified Guideline Adherence Index; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; USA, the United States of America;

Table 3.2 The components of clinical care considered by each tool, N = 16.

#	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	Any other clinical barrier/ GP rationale	Any other patient-related factor
Guideline Adherence Index studies				●	●	●	●	●	●	●	●	●	●	●
1	Komajda 2005			●	●	●	●	●	●					
2	Klimm 2008			●	●	●	●			●	●			
3	Stork 2008			●	●	●	●	●	●	●				
4	Bosch 2010			●	●	●	●			●				
5	Frankenstein 2010			●	●	●	●							
6	Oertle 2010			●	●	●	●			●			●	●
7	Zugck 2012			●	●	●	●			●				
8	Oliveira 2013			●	●	●	●	●	●	●				●
9	Luttick 2014			●	●	●	●	●	●					
10	Poelzl 2014			●	●	●	●			●	●			
11	Yoo 2014			●	●	●	●							
12	Deticek 2016				●	●	●	●	●			●		
13	Hirt 2016			●	●	●	●						●	

Table 3.2 The components of clinical care considered by each tool, N = 16, *Cont'd*.

#	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	Any other clinical barrier/ GP rationale	Any other patient-related factor
Non Guideline Adherence Index studies		●	●	●	●	●	●	●	●	●	●	●	●	
14	Popescu 2008	●		●	●									
15	Visca 2013		●	●	●	●				●				
16	Ho 2014	●			●	●	●	●	●		●	●	●	

Abbreviations: GP, general practitioner; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker).

Table 3.3 Prescription rates compared to Guideline Adherence Index for principle Heart Failure medications, N = 4.

Study	Renin-angiotensin systems inhibitors (%)		Beta-blockers (%)		Mineralocorticoid receptor antagonists (%)	
	Prescription Rate	GAI	Prescription Rate	GAI	Prescription Rate	GAI
Komajda 2005	69.0	85.4	53.0	58.0	28.0	36.0
Klimm 2008	80.0	49.0	75.0	46.0	57.0	-
Bosch 2010	61.3	58.3	54.6	47.0	24.9	31.0
Oliveira 2013	68.8	73.5	54.1	60.4	49.2	57.1

Prescription rate defined as the percentage of the total study population prescribed the medication regardless of eligibility; **Abbreviations:** GAI, guideline-adherence index defined as the proportion of eligible patients whose physicians prescribed according to the guidelines.

3.5 Discussion

The current review is the first to assess the evidence regarding standardised quantitative tools for assessment of guideline-led prescribing in HF. Four quantitative tools were identified from 16 studies, each a comprehensive approach for assessment of prescription of HF guideline-directed medical therapies. The reviewed studies encompassed different healthcare settings and different prescriber types. Furthermore, several studies reported the effect of guideline adherence on clinical outcomes.

Of the four tools identified for assessing guideline adherence, the GAI was the most frequently cited and was used predominately in Europe. The GAI only accounts for patients who are eligible for particular therapy, according to the guidelines' indications. This is a more accurate assessment of prescribing than the simple prescription rates. Moreover, the GAI has been modified to keep pace with on-going guideline changes. The Heart Failure Composite Score and the Heart Failure Scale, each considered just two HF medications – RASi and beta-blockers - as these are the therapies with the most robust evidence in HF. However, both of these tools included aspects of laboratory or diagnostic medical tests that are not taken into account by the GAI, such as examining echocardiographic evidence or serum creatinine levels before prescribing an ACE inhibitor. The IRER is the most recently described tool and is the only tool reviewed here that was developed for electronic use. [169] This tool merges the guidelines' recommendations for HF and common HF comorbidities such as chronic obstructive pulmonary disease, dyslipidaemia and atrial fibrillation, in a single list for each patient. However, it does not take into account the patient's eligibility or any contraindication to HF drug therapy. [169]

The GAI was initially developed by Komajda and colleagues in 2005 as a means to quantify prescribing quality for HF patients in Europe. [46] However, this original GAI has some limitations. That is why Stork *et al.* and Klimm *et al.* modified the GAI to include target dose and contraindications to therapy. [176, 180] Bosch *et al.* [175] and Deticek *et al.* [179] considered the issue of HF licenced medications as part of guideline adherence. Each of these modifications has increased the complexity of the GAI and enhanced its ability to differentiate from standard drug utilisation rates.

Most recently, Hirt *et al.* [164] and Oertle *et al.* [173] included a qualitative aspect in their GAI studies and showed that GAI is significantly higher when quantitative as well as qualitative patient data are considered. This supports previous data showing that patient and prescriber factors may be important barriers to guideline adherence. [157] These barriers included the complexity of treatment in the elderly, patient's multiple comorbidities or low socio-economic status. However, these barriers were different from those barriers identified in the SHAPE study. [155] The latter emphasised the prescriber lack of knowledge and education as significant contributors to guideline non-adherence.

Although the mean overall GAI score was moderate, fluctuation in GAI scores might be influenced by the changing definitions of GAI [46, 173, 179] or due to the wide variation in clinical practice between countries. [46, 173] This moderate GAI score demonstrates that there is an excellent scope for optimising HF prescribing internationally. In two studies reported here, guideline adherence by cardiologists was better to that of GPs. The rates reported for both types of prescriber in this review are considerably higher than those reported in the 2008 New England Healthcare Institute report [181], that showed guidelines adherence of 70% for cardiologists and 47% for GPs in cardiac disease management in the USA. The higher guideline

adherence rates reported in this review may indicate greater dissemination and acceptability of HF guidelines and diminishing barriers to guideline adherence in Europe in the intervening period. The increasing proportion of High-GAI rates reported from 2005 to 2016 supports this. However, there is still room for optimising target dose prescribing as the combined levels of target dose achievement in this review were lower than those reported recently by Barywani *et al.* [154]

There are limitations to the GAI approach. The method has typically been applied at a population level to examine prescribing patterns. No study reported here examined the role of the GAI in near-patient assessment; initiatives to improve guideline adherence or how pharmacists or other members of the healthcare team may implement the GAI to improve the care of complex HF patients. Also, while it is clear that optimal use of guideline-directed medical therapies improves HF care, the data presented in this meta-analysis of observational data are not unanimous in demonstrating a robust association between GAI and clinical outcomes. The GAI is a flexible measure, and it seems possible that there is scope to improve GAI scores further. Deticek *et al.* [179] and Oertle *et al.* [173] have shown that there is potential for a 10-15% improvement by identifying patients where no barriers to prescribing exist. However, an electronic tool such as the IRER may be better placed to review patients in the clinical setting and to maximise patient-appropriate guideline adherence. [169]

3.6 Conclusion

Several tools have been developed to measure guideline adherence in HF. The GAI and its respective modifications represent a comprehensive and practical approach for assessment of guideline-led prescribing in HF. The GAI offers a reliable quantitative tool when compared to

the simple prescription rates. Future work may focus on overcoming the barriers to guideline adherence in order to improve prescribing quality for HF patients.

3.7 Acknowledgements

The authors would like to thank Professor John Browne, School of Epidemiology and Public Health, University College Cork for reviewing the systematic review protocol and his guidance in the choice of the quality assessment tool and the final review of this work.

3.8 Addendum

Update the systematic review search research

3.8.1 Aim

A systematic review entitled *''A tool for assessment of heart failure prescribing quality: a systematic review and meta-analysis''* was conducted in April 2016 and published in 2018 (Chapter 3). [147] The aim of this section is to repeat the search in order to update the thesis.

3.8.2 Methods

The search was conducted in April 2019 using the same search strategy as was used in April 2016. The same search terms were used as the first search of April 2016. The same databases searched, with one exception, EBSCO, which was no longer available in the research institution. Any full-text studies that were suitable for inclusion were quality appraised using GRACE tool. [163]

3.8.3 Results

The updated search results are outlined in Figure 3.5. A total of 1,701 titles were identified through the updated search, of which 931 were duplicates. Following title and abstract review, 86 studies were identified for full-text review. Of these, four studies met the inclusion criteria as outlined in the original review (Appendix 3). [47, 48, 93, 182] The reason for excluding the other studies was the absence of a prescribing review tool. The four studies included were of high quality according to GRACE criteria. [163]

All four included studies used a new tool developed by Komajda and colleagues. [93] The QUALIFY adherence score included all HF medications that are recommended by the ESC 2016 guidelines. The full list of QUALIFY medications and the circumstances in which they are used is described in Table 3.4. The QUALIFY tool differs from the GAI in that it incorporates newer HF medications such as ivabradine and ARNi and outlines the exact circumstances in which these agents should be prescribed in line with the ESC 2016 guidelines. [93] This tool was used in all four reports of the QUALIFY international registry published in the period 2016 to 2019. [47, 48, 93, 182]

The QUALIFY score was defined as the ratio of the treatment actually prescribed to the treatment that should have been theoretically prescribed. The tool took into account the patient's eligibility, guideline-based contraindications to the indicated guideline-directed medical therapies and the use of ≥ 50% of the recommended target dosage for each medication. The score quantified the physician's prescribing and not the patient's adherence behaviour. For each of the indicated medicines, a score was allocated as follows: 0 points for non-prescription of an indicated medicine in the absence of contraindications, 0.5 points for the prescription of a medication at < 50% of the recommended target dose, or 1 point for the prescription of a medication at ≥ 50% of the recommended target dosage. Physician's QUALIFY scores ranged from 0% (very poor), to 100% (excellent) and were defined at three tertiles: good adherence (QUALIFY score = 100%); moderate adherence (QUALIFY score from > 50% to < 100%); and poor adherence (QUALIFY score ≤ 50%).

3.8.4 Conclusion

This update of the systematic review search identified the QUALIFY score, a new tool for assessing the implementation of the guidelines' prescribing recommendations.

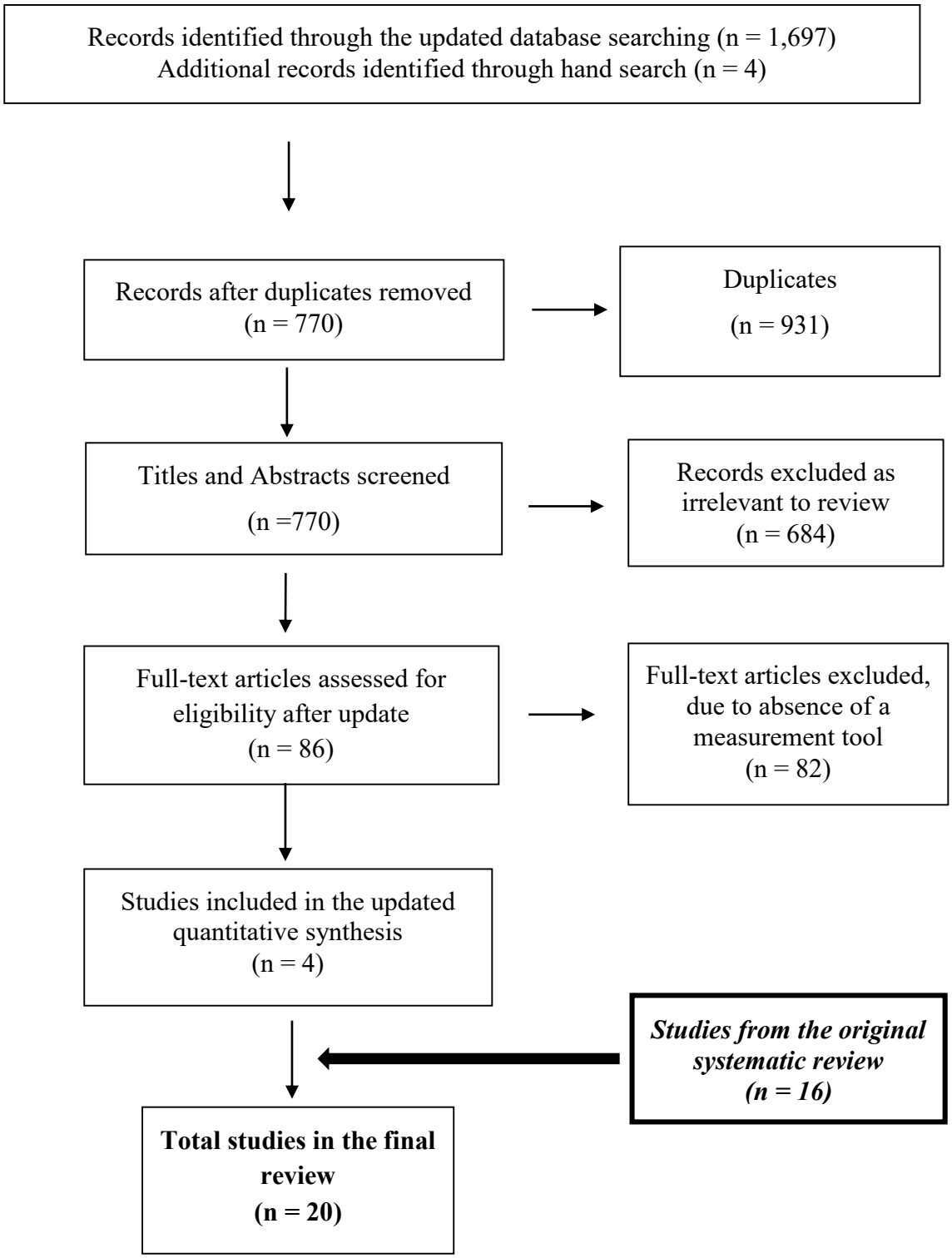


Figure 3.5 Updated PRISMA flowchart of the updated search.

Table 3.4 Algorithm of computing QUALIFY score.

Medication class	QUALIFY criteria
Renin-angiotensin system inhibitor (ACE inhibitor, angiotensin-II receptor blocker or angiotensin receptor-neprilysin inhibitor)	The guidelines are met if: (i) the patient is prescribed RASi or (ii) the patient is not prescribed RASi but has a documented contraindication to RASi or (iii) the patient is prescribed ARNi in case of ACE inhibitors' intolerance besides the baseline guideline-directed medical therapies of HF as outlined in the ESC 2016 guidelines
Evidence-based beta-blocker	The guidelines are met if: (i) the patient is prescribed an EBBB or (ii) the patient is not prescribed an EBBB but has a documented contraindication to EBBB and then prescribed an ivabradine as an alternative in presence of sinus rhythm.
Mineralocorticoid receptor antagonist	The guidelines are met if: (i) the patient is prescribed an MRA or (ii) the patient is not prescribed an MRA but has a documented contraindication to MRA.

Abbreviations: ARNi, angiotensin receptor-neprilysin inhibitor; EBBB, Evidence-based beta-blocker; ESC, European Society of Cardiology; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor.

Table 3.5 Updated *(Table 3.2)*: The components of clinical care considered by each tool after the inclusion of QUALIFY score, N = 17.

#	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	Any other clinical barrier/ GP rationale	Any other patient-related factor
Guideline Adherence Index studies				●	●	●	●	●	●	●	●	●	●	●
1	Komajda 2005			●	●	●	●	●	●					
2	Klimm 2008			●	●	●	●			●	●			
3	Stork 2008			●	●	●	●	●	●	●				
4	Bosch 2010			●	●	●	●			●				
5	Frankenstein 2010			●	●	●	●							
6	Oertle 2010			●	●	●	●			●			●	●
7	Zugck 2012			●	●	●	●			●				
8	Oliveira 2013			●	●	●	●	●	●	●				●
9	Luttick 2014			●	●	●	●	●	●					
10	Poelzl 2014			●	●	●	●			●	●			
11	Yoo 2014			●	●	●	●							
12	Deticek 2016				●	●	●	●	●			●		
13	Hirt 2016			●	●	●	●						●	

Table 3.5 ***Updated (Table 3.2):*** **The components of clinical care considered by each tool after the inclusion of QUALIFY score, N = 17,** ***Cont'd.***

	Study by year	Any medical investigation	Any lab tests	Eligibility of prescription	RASi	Beta-blocker	Mineralocorticoid receptor antagonist	Diuretics	Digoxin	Contra-indications	Target Dosing	Heart failure licenced agents	barrier/ GP rationale	Any other clinical	Any other patient-related factor
Non Guideline Adherence Index studies		●	●	●	●	●	●	●	●	●	●	●	●	●	
14	Popescu 2008	●		●	●										
15	Visca 2013		●	●	●	●				●					
16	Ho 2014	●			●	●	●	●	●		●	●		●	
17	Komajda 2016			●	●	●	●	●	●	●	●	●			

The newly included tool is highlighted in grey colour. **Abbreviations:** GP, general practitioner; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker).

4 Chapter 4

Guideline-Led Prescribing to Ambulatory Heart Failure Patients in a Cardiology Outpatient Service in Ireland

This chapter aims to study prescribing quality in Cardiology outpatient practice in Cork City. The study identified several important factors to improve use and uptitration of the guideline-directed medical therapies. Evidence from this study reflects HF management in routine clinical practice in absence of an HF-specific DMP.

4.1 Abstract

4.1.1 Introduction

Guidelines recommend HF patients be treated with multiple medications at appropriate doses proven to improve clinical outcomes. In absence of DMP, the degree to which gaps in medication use and dosing persist in contemporary outpatient practice is unclear.

4.1.2 Aims

To study a contemporary Irish outpatient HF cohort and explore patterns of guideline-led prescribing and potentially inappropriate prescribing in HF.

4.1.3 Methods

A prospective observational study of ambulatory HF patients at the Cardiology Outpatient Clinics of Mercy University Hospital, Cork City, Ireland between March 2016 and February 2017. Guideline-led prescribing was assessed using the GAI-3, which takes into account prescribing of RASi; EBBB and MRA. The adjusted GAI-3 takes into account patient's contraindications to these medications. The GAI-based target dose considered the prescription of ≥ 50% of the recommended target dose of each of the medication classes as adherence to the guidelines. High-GAI based management was achieved by prescription of ≥ 2 GAI medicines. Potentially inappropriate prescribing was assessed using the PIMHF tool.

4.1.4 Results

During the study period, 127 HF patients (mean ± SD age 71.7 ± 13.1 years; 65.3% male) attended the Cardiology Outpatient Clinics. Heart Failure with reduced ejection fraction was the predominant HF phenotype (59.7%). Loop diuretics were prescribed to 85 (67.0%) patients. Prescription rates for RASi, EBBB and MRA were 86 (67.7%), 98 (77.2%) and 33 (26.0%) patients, while the achievement of ≥ 50% target dose of each class was 67 (52.7%), 60 (47.2%) and 24 (18.9%), respectively. Twelve HF patients had at least one contraindication to EBBB therapy; however, nine of these were prescribed an EBBB. Population mean GAI-3 was 56.6%. When contraindications to therapy are taken into account, the adjusted GAI-3 increased to 57.3%. The GAI-based on prescribing ≥ 50% of the recommended target-dose was equal to 39.6%. High-GAI based management was prescribed to 80 patients (63.0%). High-GAI patients were more likely to have HFrEF (67.5% vs 36.2%, *p-value* < *0.001*) and to achieve the target BP (89.4% vs. 73.7%, *p-value* < *0.05*) than patients with Low-GAI based management. A PIMHF item was prescribed to 25 (19.7%) patients. The most frequently used PIMHF was non-dihydropyridine CCB (n = 15, 11.8%).

4.1.5 Conclusion

Most HF patients in this setting receive optimal guideline-directed medical therapies; however, the proportion of patients reaching the target doses was suboptimal. There is an opportunity to improve outcomes for ambulatory patients with HF through a focus on optimising target dose achievement where appropriate.

4.2 Introduction

The clinical practice guidelines recommend the prescription of HF guideline-directed medical therapies at target doses as the most effective way to ensure the delivery of optimal HF care. [1, 48] Physician's adherence to guideline-led prescribing is consistently associated with improved clinical outcomes. In the QUALIFY survey, high adoption of guideline-led prescribing was associated with a 50% reduction in all-cause mortality and a 32% reduction of HF-related rehospitalisation when compared to moderate or poor adoption. [48] In the BIOSTAT-CHF registry, patients with under-dosing of RASi and beta-blockers experienced increased mortality risk compared to patients who achieved the target dose of these agents. [76]

Nevertheless, several studies demonstrated suboptimal adherence to HF guideline-led prescribing in routine clinical practice. [48, 76, 86] The CHAMP-HF study showed that guideline-directed medical therapies were not prescribed to over one-third of ambulatory HF patients despite their eligibility and the absence of contraindications. [86] Also, when patients do receive the recommended medications, they often receive the medications at a dose lower than the guideline-recommended one. [84] In one study, just 1% of the ambulatory HF patient population received the target dose of all three guideline-directed medical therapies that RASi, EBBB and MRA. [86] Elsewhere, just 50% of HF patients reached the recommended target dose three months post-discharge. [76]

Guideline-led prescribing in HF may be challenging due to patients' age [183], gender [143], low BP [146], renal dysfunction [146], the presence of pulmonary disorders [184] or the complexity of the medication regimens. [185] A national study in the United Kingdom showed that poor pulmonary functions limited beta-blockers prescription in 11% of otherwise eligible HF

patients. [184] Elsewhere, 40% of HF patients were not prescribed the indicated RASi at discharge due to reduced renal functions. [146]

Furthermore, the presence of multimorbidity increases the complexity of medication regimens and the likelihood of potentially inappropriate medications prescription. [99, 100, 183] There is clear evidence of the harmful effects of certain medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and non-dihydropyridine CCB on HF prognosis and outcomes. [102, 112] Prescription of these medications reduces patient's quality of life, contradicts the effects of the guideline-directed medical therapies and consequently increases the risk of hospitalisation and mortality. [99, 102, 112] In one study, NSAIDs and non-dihydropyridine CCBs were prescribed to 11% and 21% of HF patients, respectively. [186] In another ambulatory HF population, 14.5% were prescribed at least one potentially inappropriate medication despite being cared for in an HF-specific DMP. [112]

4.2.1 Aims

This study will evaluate guideline-led prescribing to HF patients in a contemporary Irish ambulatory setting based on recommendations of the ESC 2012 guidelines [9] and study the gap to achieve the ESC 2016 guidelines application. [1] Also, the study will determine the prevalence of potentially inappropriate medications in HF context and their effect, if any, on guideline-led prescribing.

4.3 Methods

Ethics approval for the study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and University College Cork (UCC), Reference number ECM4 (o) 12/4/16, (Appendix 4). This is a prospective observational single-centred chart review reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. [187]

The study included all ambulatory HF patients aged ≥ 18 years presenting for a scheduled appointment in Cardiology Outpatient Clinics in the Mercy University Hospital (MUH), Cork, Ireland from March 2016 to February 2017. Where patients attended the clinics on more than one occasion over the study period, their first visit was the only visit recorded in the study. The diagnosis and type of HF were based on data recorded in the patient's medical chart. Heart Failure with reduced ejection fraction was defined as an EF < 50% while HFpEF was defined as an EF ≥ 50%. [9]

Data accessed in the patient's medical chart included age, gender, comorbidities, EF, BP, HR and laboratory investigations. The recent patient's BP, EF, HR and laboratory investigations were recorded if they had been documented in the medical chart at any time in the six months before the appointment date. The following information on prescribed medications was also accessed in the medical chart: drug name, dose and frequency (Appendix 5).

The ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 were used in this study as they are the guidelines that were in place at the initiation of this work. [9] Achievement of target HR was defined as an HR ≤ 70 beats/minute. [1, 9] Target BP achievement was defined as BP ≤ 150/90 mmHg. [188] The 50 – 99% and 100% target dose of

RASi, EBBB and MRA were defined as per ESC 2012 guidelines (Table 4.1). [9] Hyperpolypharmacy was defined as the prescription of ≥ 10 regular medications per day. [189] Hyperpolypharmacy was used as a measure of medication burden as this population is prescribed a high number of medications, both for HF and for comorbidities. [189]

The primary outcome of the study was to assess HF guideline-led prescribing using the GAI-3 [46], the adjusted GAI-3 [176] and the GAI-based target dose according to ESC 2012 recommendations. [179] The GAI-3 was computed as the ratio of the treatment actually prescribed to the treatment that should theoretically have been prescribed regarding the recommended evidence-based medications: RASi (ACE inhibitor or angiotensin-II receptor blocker), EBBB and MRA. [9, 46] The EBBBs included in the ESC guidelines were bisoprolol, carvedilol, metoprolol succinate, and nebivolol. The adjusted GAI-3 considered the relative and absolute contraindications to the aforementioned medications as outlined in the ESC guidelines (Table 4.1). [9, 176] The GAI-based target dose was calculated, taking into consideration the prescription of ≥ 50% of the guideline-recommended target dose of each of the three GAI medicines as adherence to the guidelines (Table 4.1). [9, 179] Finally, the study population was split into those with High-GAI based management; that is the prescription of ≥ 2 GAI medicines (RASi, EBBB or MRA) and those with Low-GAI based management; that is the prescription of ≤ 1 GAI medicine. [147]

The secondary outcome of the study was to identify the gap between 2012 guideline-led prescribing and 2016 guideline-led prescribing and its effects, if any, on GAI figures. The major changes into the ESC 2016 guidelines are (i) the new cut points of HFrEF as EF < 40%; HFmrEF as EF equals to 40 to 49%; and HFpEF as EF ≥ 50%; (ii) the introduction of the new medication class ARNi which is a combination of sacubitril, neprilysin inhibitor and valsartan,

ARB. According to the recent guidelines, ARNi has deemed a part of RASi as a reasonable alternative of ACE inhibitors for symptomatic patients despite optimal medical therapy by ACE inhibitor, EBBB and MRA at target or maximally tolerated doses. [1, 48] The definitions of target doses, target HR and target BP, have not been changed in the recent ESC guidelines. [1]

The tertiary outcome was to determine the prevalence of potentially inappropriate prescribing using the disease-specific PIMHF tool. [112] This is a list of 11 medications considered to be potentially harmful when used in HF patients (Appendix 1). [112] Only medications prescribed regularly were included in the PIMHF analysis. Medications prescribed on an *"as required"* basis were not included as there was no clear indication of how often the patient took these medications.

4.3.1 Statistical analysis

Data are presented as mean ± SD or number (%), as appropriate. Continuous data were compared using the independent Student's t-test. Categorical data were compared using the Chi-square test or Fisher-exact test. All tests are two-tailed, and a *p-value* of < 0.05 was regarded as statistically significant. The clinical factors associated with (i) High-GAI achievement, and (ii) PIMHF prescription were determined using a univariable and multivariable logistic regression. The odds ratios (OR) and 95% confidence intervals (CI) of the multivariable analysis adjusted to age and sex are reported here. Data were analysed using SPSS® version 22.0 for Microsoft® Windows 10.

Table 4.1 Contraindications to and the recommended daily target dose of the Heart Failure recommended medications as outlined in the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012. [9]

Medication class	Contraindications	Agents	100% Target Dose (mg/day)
Renin-angiotensin system inhibitors (ACE inhibitor, angiotensin-II receptor blocker)	• History of angioedema • Known bilateral renal artery stenosis • Pregnancy/risk of pregnancy.	Ramipril Lisinopril Perindopril arginine Candesartan Losartan Olmesartan Valsartan	10 20 5 32 150 20 320
Evidence-based beta-blockers	• Second- or third-degree AV-block. • Asthma: *COPD is a contraindication*	Bisoprolol Nebivolol	10 10
Mineralocorticoid receptor antagonists	• Eplerenone use with strong cytochromes inhibitors	Spironolactone Eplerenone	50 50

Agents listed are those agents from each class that were prescribed to one or more patients in the study population. **Abbreviations:** ACE, angiotensin-converting enzyme; AV-block, atrioventricular block; COPD, chronic obstructive pulmonary disease.

4.4 Results

4.4.1 Baseline profile and characteristics of Heart Failure patients

Over the study period, 127 HF patients attended the Cardiology Outpatient Clinics at MUH. The mean ± SD age of the patients was 71.7 ± 13.1 years, and 83 (65.3%) were male (Table 4.2). Heart Failure with reduced ejection fraction was the predominant HF type (n = 71, 59.7%). An echocardiogram was available for 102 patients and mean ± SD EF was 40.2% ± 14.2%. All patients had more than one comorbidity, and the mean number of comorbidities was 7.4 ± 2.7. Hypertension was the most frequently occurring comorbidity (n = 79, 66.2%), followed by atrial fibrillation (n = 66, 51.9%). Coronary artery disease affected 39 patients (30.7%), (Table 4.2).

4.4.2 Prescribing to Heart Failure population

Eight patients (6.3%) were not prescribed any HF guideline-directed medical therapy. A single HF drug was prescribed to 13 patients (10.2%) of whom, seven patients (5.5%) were prescribed an EBBB as the single HF therapy. Loop diuretics were prescribed to 85 patients (67.0%) of whom, six patients (4.7%) were prescribed two different loop diuretics concurrently.

Prescription rates for GAI medicines were RASi (n = 86, 67.7%), EBBB (n = 98, 77.2%), and MRA (n = 33, 26.0%), (Table 4.3). A combination of two GAI medicines was prescribed concurrently to 57 patients (44.9%), and all three medicines were prescribed to 23 patients (18.1%) concurrently. Prescription of 50% - 99% of the guideline-recommended target doses of RASi, EBBB and MRA was achieved in 27 (21.2%), 29 (22.8%), and 23 (18.1%) of patients (Figure 4.1). The 100% target dose was achieved in 40 (31.5%), 31 (24.4%), and one (0.7%)

patients, respectively. Ten patients (7.8%) achieved 50% - 99% recommended target doses of all three GAI medicines. No patient achieved 100% target dose of all three GAI medicines.

No patient experienced a contraindication to RASi or MRA. A contraindication to EBBB therapy was present in 12 patients (9.4%), 11 patients (8.7%) having asthma and one patient (0.8%) having an AV-block. Nine of the 12 patients with the contraindication was prescribed an EBBB.

Population mean GAI-3 was 56.6%. When contraindications to therapy are taken into account, the adjusted GAI-3 increased to 57.3%. Population GAI-3 based on prescribing ≥ 50% of the target-dose was equal to 39.6%. There was a significant difference in the achievement of GAI-3 between HFrEF and HFpEF patients (64.9% vs 50.0%, *p-value < 0.001*), (Figure 4.2.A). Target HR was achieved in 40 patients (31.5%) only (Table 4.3). Despite EBBB use, 17 patients (13.4%) in sinus rhythm remained off-target and then were eligible for ivabradine prescription; however, ivabradine was prescribed to four patients (3.1%) only.

4.4.3 High-GAI and Low-GAI achievement

High-GAI was prescribed to 80 patients (63.0%), (Table 4.2 and 4.3). Patients with High-GAI were more likely to have HFrEF (67.5% vs 36.2%, *p-value < 0.001*). This cohort was more likely to be managed by hyperpolypharmacy (37.5% vs 19.1%, *p-value = 0.040)*. Patients with High-GAI were also more likely to achieve ≥ 50% of the target dose of each of the three guideline-directed therapies individually than those with Low-GAI, *p-value < 0.05* (Figure 4.1). Heart Failure patients having High-GAI based management were more likely to achieve the target BP (73.9% vs 59.5%, *p-value < 0.05*) and the target HR in the presence of EBBB prescription (31.5% vs 8.5%, *p-value < 0.001*) than patients with Low-GAI (Table 4.3).

4.4.4 Implementation of the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016

The implementation of the ESC 2016 guidelines has changed the breakdown of HF patients as 49 patients (48.0%) were categorised as HFrEF (EF < 40%), 13 patients (12.7%) as HFmrEF (EF = 40 - 49%) and 40 patients (39.2%) as HFpEF (EF ≥ 50%) according to the available data of patient's echocardiogram. In comparison to the ESC 2012 guidelines, the overall GAI-3 was not changed by the consideration of the ESC 2016 guidelines' recommendations as ARNi was not prescribed to any patient. Also, the new breakdown of EF did not affect prescribing towards HFpEF patients but reduced the GAI figures in the new HFrEF, and HFmrEF in comparison to the old EF cut point of 50% (Figure 4.2).

4.4.5 Potentially inappropriate prescribing

Potentially inappropriate medications identified by the PIMHF tool were prescribed to 25 patients (19.7%), (Table 4.3). Two patients were prescribed two different PIMHF items. The most frequently prescribed PIMHF item was non-dihydropyridine CCBs in 15 patients (11.8%). Of which, seven HFrEF patients (5.5%) were prescribed a non-dihydropyridine CCB, and twelve patients (9.4%) had a concurrent prescription of EBBB and non-dihydropyridine CCB. There was no difference in PIMHF prescribing rates between High-GAI and Low-GAI patient, *p-value > 0.05* (Table 4.3).

4.4.6 Logistic regression analysis

Adjusted to age, sex, serum potassium, asthma/chronic pulmonary disease, diabetes and chronic kidney disease, the multivariable analysis estimated HFrEF as the only clinical associate of High-GAI based management achievement (OR 4.8, 95% CI 1.27 – 18.04), (Table

4.4). The multivariable analysis of PIMHF, adjusted to age, sex and serum potassium, estimated asthma/chronic obstructive pulmonary disease (OR 3.73, 95% CI 1.00 – 13.84) and increased HR (OR 1.04, 95% CI 1.01 – 1.07) as the multivariable associates of PIMHF prescription (Table 4.4).

Table 4.2 Characteristics of the total population, patients prescribed High-GAI and patients prescribed Low-GAI, N = 127 patients.

	Total population n = 127	**High-GAI n = 80**	**Low-GAI n = 47**	*p-value*
Age (years)	71.7 ± 13.1	69.9 ± 13.7	73.1 ± 11.8	*0.381*
Male	83 (65.3)	54 (67.5)	29 (61.7)	*0.373*
Mean arterial pressure (mmHg)	92.7 ± 13.3	92.1 ± 12.3	93.7 ± 15.1	*0.693*
Heart rate (beat/minute)	79.3 ± 18.3	80.1 ± 19.7	77.8 ± 15.9	*0.719*
Serum potassium	4.7 ± 0.9	4.8 ± 1.1	4.7 ± 0.8	*0.918*
Ejection fraction (%) ¶	40.2 ± 14.2	37.6 ± 13.2	45.0 ± 15.1	*0.021*
HFrEF ◦ †	71 (55.9)	54 (67.5)	17 (36.2)	*< 0.001*
Hypertension	79 (62.2)	50 (62.5)	29 (61.7)	*0.767*
Atrial fibrillation	66 (51.9)	41 (51.3)	25 (53.2)	*0.348*
Coronary artery diseases	39 (30.7)	23 (28.8)	16 (34.0)	*0.523*
Diabetes	28 (22.0)	18 (22.5)	10 (21.3)	*0.481*
Chronic kidney disease	21 (16.5)	8 (16.3)	13 (17.0)	*0.888*
Asthma	11 (8.7)	7 (8.8)	4 (8.5)	*0.786*
Chronic obstructive pulmonary disease	23 (18.1)	13 (16.3)	10 (21.3)	*0.381*
Number of comorbidities	7.4 ± 2.7	7.4 ± 2.9	7.4 ± 2.6	*0.769*

Comparisons were made between Heart Failure patients with High-GAI and Low-GAI. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation. ¶ Echocardiogram was available for 102 patients. ◦ Data according to the documented diagnosis of HF type in patients' medical charts (n =119). **Abbreviations**: HFrEF, heart failure with reduced ejection fraction.

Table 4.3 Medication profile and therapeutic target goals of the total population, patients prescribed High-GAI and patients prescribed Low-GAI, N = 127 patients.

	Total population n = 127	**High-GAI n = 80**	**Low-GAI n = 47**	*p-value*
Heart Failure Medications Profile				
RASi	86 (67.7)	74 (92.5)	12 (25.5)	*< 0.001*
Evidence-based beta-blocker	98 (77.2)	79 (98.8)	19 (40.4)	*< 0.001*
Mineralocorticoid receptor antagonist	33 (26.0)	30 (37.5)	3 (6.4)	*< 0.001*
Digoxin	8 (6.3)	6 (7.5)	2 (4.8)	*0.716*
Loop diuretic	85 (67.0)	59 (73.8)	26 (55.3)	*0.028*
Thiazide diuretic	11 (8.7)	3 (3.8)	8 (17.0)	*0.031*
Ivabradine	4 (3.1)	3 (3.8)	1 (2.4)	*0.635*
Regular medications	8.2 ± 3.1	8.6 ± 3.0	7.5 ± 3.1	*0.218*
Hyperpolypharmacy	39 (30.7)	30 (37.5)	9 (19.1)	*0.040*
Device-based therapy [§]	18 (14.2)	12 (15.0)	6 (13.1)	*0.361*
Potentially Inappropriate Medicines in Heart Failure				
Any PIMHF medication	25 (19.7)	14 (17.5)	11 (23.4)	*0.736*
Non-dihydropyridine CCB	15 (11.8)	7 (8.8)	8 (17)	*0.253*
Oral Corticosteroid	5 (3.9)	3 (3.8)	2 (4.3)	*0.091*
Pregabalin	5 (3.9)	3 (3.8)	2 (4.3)	*0.271*
NSAID	1 (0.8)	1 (1.3)	0 (0.0)	*0.819*
Metformin in poor renal functions [ι]	1 (0.8)	1 (1.3)	0 (0.0)	*0.989*
Target therapeutic goals				
Target heart rate (≤ 70 bpm)	40 (31.5)	25 (37.3)	15 (37.5)	*0.051*
Target heart rate on EBBB	29 (22.8)	25 (35.7)	4 (9.5)	*< 0.001*
Target heart rate on EBBB ≥ 50 target dose	16 (12.6)	13 (16.3)	3 (8.1)	*0.067*
Target blood pressure (≤ 150/90mmHg)	87 (68.5)	59 (89.4)	28 (73.7)	*0.022*

Comparisons were made between Heart Failure patients with High-GAI and Low-GAI. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation. [§] Device-based therapy: implantable cardiac defibrillator, cardiac resynchronisation therapy or left ventricular assist device; [\] Poor renal functions: creatinine clearance < 50 mg/ml. **Abbreviations**: CCB, calcium channel blocker; EBBB, evidence-based beta-blocker; MRA, mineralocorticoid receptor antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; PIMHF, potentially inappropriate medicines in heart failure; RASi, renin-angiotensin systems inhibitor (ACE inhibitor or angiotensin-II receptor blocker).

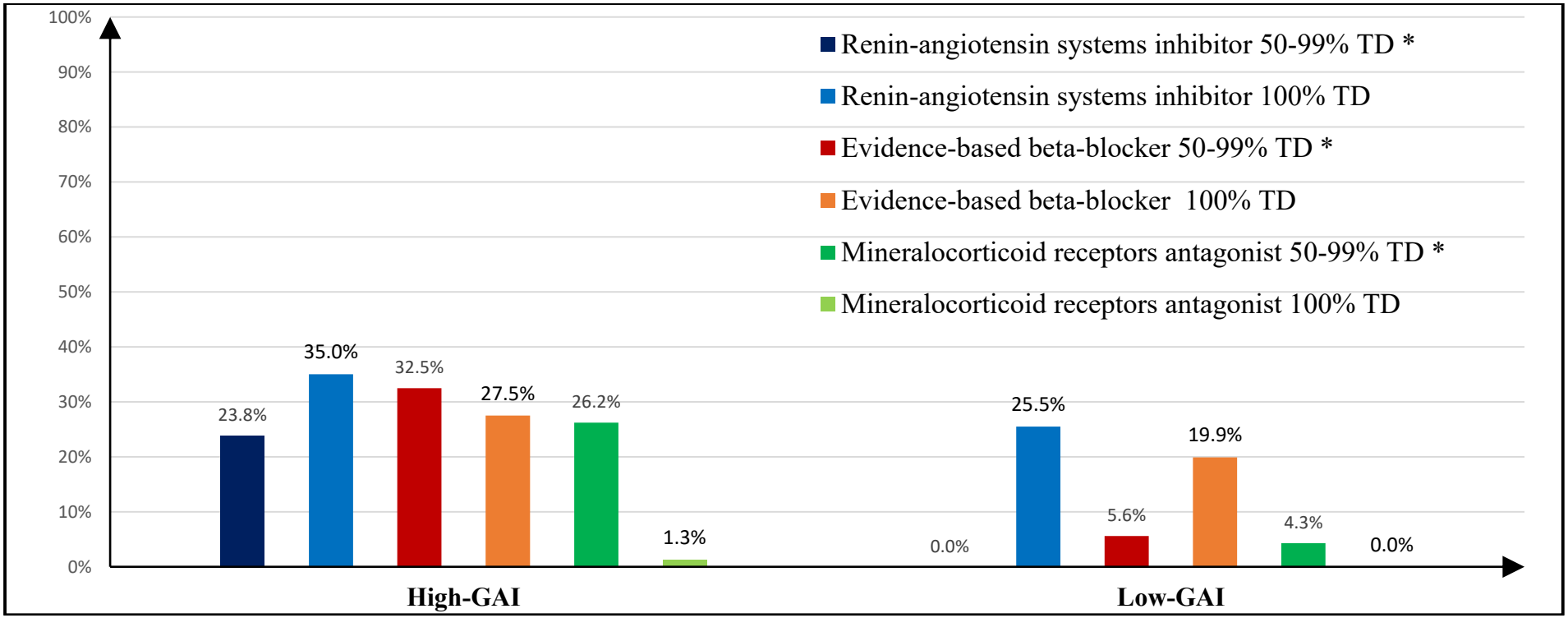


Figure 4.1 Prescription rates of the ≥ 50% and 100% of the recommended target doses of the guideline-directed medical therapies among heart failure patients prescribed a High-GAI and Low-GAI based management.

The proportion of patients prescribed 50-99% target dose of each medication class was compared between High-GAI and Low-GAI populations. This comparison for each of the three GAI medicines was statistically significant *(p-value < 0.001)*.

The proportion of patients prescribed 100% target dose of each medication class was compared between High-GAI and Low-GAI populations. This comparison for each of the three GAI medicines was not statistically significant *(p-value > 0.05)*.

* indicate a significant *p-value < 0.05*. The target dose is defined in Table 4.1. **Abbreviations**: GAI, guideline adherence index; TD, target dose.

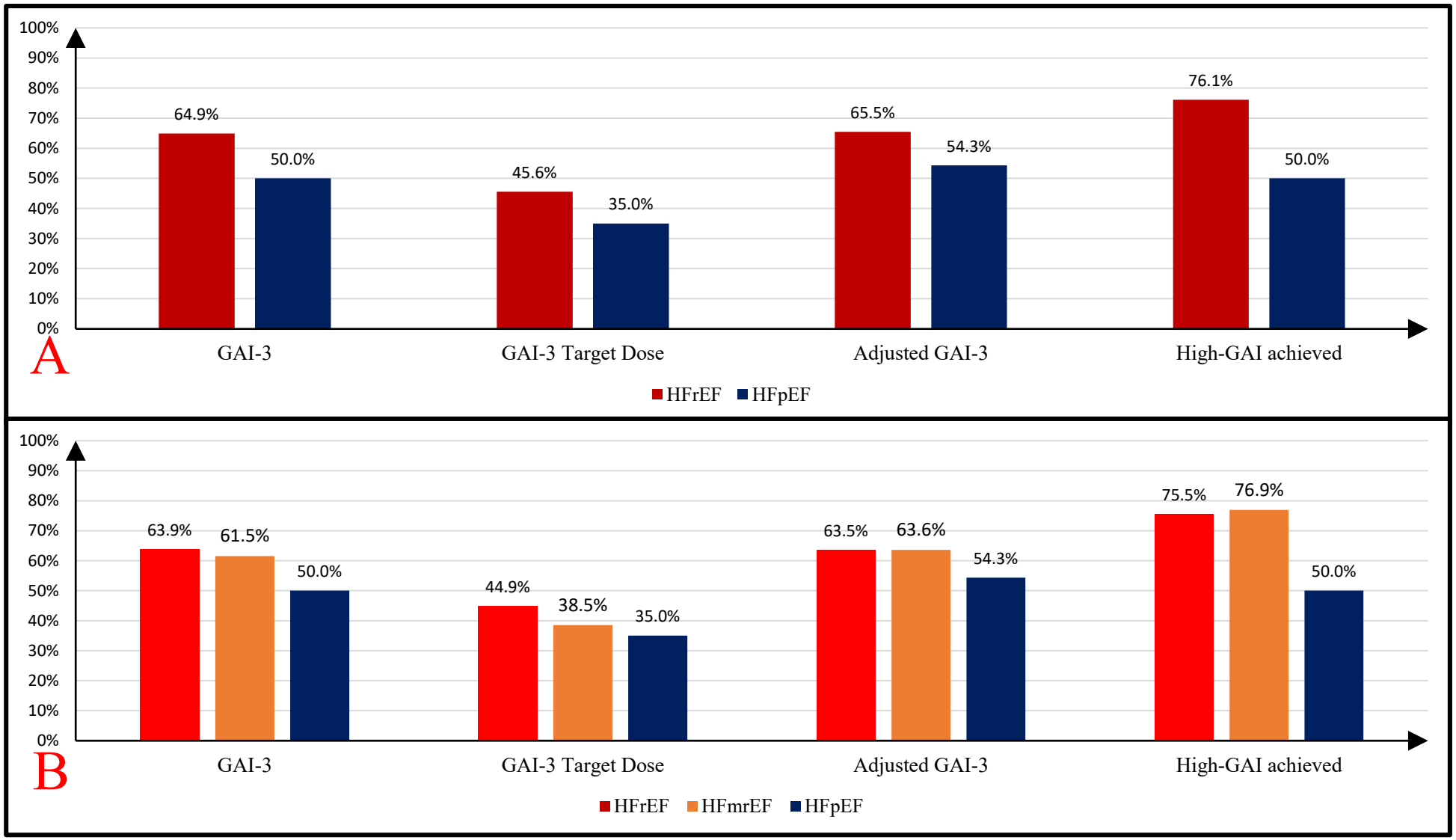


Figure 4.2 Guideline adherence indices among Heart Failure patients, N = 102 patients.

Figure 4.2.A, Guideline Adherence Indices among Heart Failure patients classified as reduced ejection fraction (EF < 50%, n = 62) versus preserved ejection fraction (EF ≥ 50%, n = 40) according to ESC 2012 guidelines. [9]

Figure 4.2.B, Guideline Adherence Indices among Heart Failure patients classified as reduced ejection fraction (EF < 40%, n = 49) versus mid-range ejection fraction (EF = 40 – 49, n = 13) versus preserved ejection fraction (EF ≥ 50%, n = 40) according to ESC 2016 guidelines. [1]

Abbreviations: GAI, guideline-adherence index; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 4.4 Clinical factors associated with High-GAI achievement and potentially inappropriate prescribing towards ambulatory patients, N = 127 patients.

Variable	High-GAI achieved	PIMHF item prescribed
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Age	1.008 (0.951 – 1.068)	1.018 (0.962 – 1.078)
Male	2.707 (0.768 – 9.543)	1.004 (0.261 – 3.859)
Heart rate	1.006 (0.976 – 1.038)	1.037 (1.005 – 1.069)
Serum potassium	0.758 (0.439 – 1.311)	1.016 (0.541 – 1.906)
Asthma/COPD	0.595 (0.165 – 2.144)	3.728 (1.004 – 13.844)
Diabetes	0.683 (0.151 – 3.090)	2.882 (0.602 – 13.799)
Chronic kidney disease	0.755 (0.154 – 3.698)	0.628 (0.120 – 3.29)
HFrEF	4.804 (1.279 – 18.049)	1.131 (0.249 – 5.145)
Hyperpolypharmacy		0.529 (0.101 – 2.734)

The multivariable logistic models of (i) High-GAI achievement *(Nagelkerke's R^2 = 0.215; percentage of correct estimation = 77.3%)* and (ii) PIMHF prescribing *(Nagelkerke's R^2 = 0.286; percentage of correct estimation= 82%).*

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; GAI, guideline adherence index; HFrEF, heart failure with reduced ejection fraction, OR, odds ratio; PIMHF, potentially inappropriate medicines in heart failure.

4.5 Discussion

The present study is the first assessment of guideline-led prescribing using structured prescribing review tools, in an Irish ambulatory HF population cared for outside a DMP in an acute general hospital. The results showed that two-thirds of the population were prescribed the guideline-directed medical therapies. The mean GAI-3 was 56.6%; however, when this was adjusted to include target dose achievement, it decreased to 40%. One-in-five of the population was prescribed an HF-specific potentially inappropriate medication.

The prescription rates of RASi, EBBB and MRA as individual classes are higher here than in studies performed in the early 2000s [180, 190] and are comparable to more recent reports from other Western European countries. [164, 191] At 56.6%, the GAI-3 of the current population is moderately lower than the international mean GAI-3 of 63%. [147] According to a recently published systematic review (Chapter 3), this GAI-3 is comparable to the GAI-3 figures from other Western European countries such as the Netherlands (52.3%) and Germany (53.5%) in 2016. [147]

In the current setting, consideration of the contraindications had a little effect on correcting the guideline adherence levels. Although 75% of asthmatic patients were prescribed an EBBB, it is of note that asthma is a relative contraindication to EBBB use according to the guidelines. [1, 9] The ESC guidelines strongly recommend the use of EBBB in HF in order to improve patient's quality of life and reduce mortality risk. [1, 9] This means that the benefits of EBBB use in the current HF patients might outweigh its risk of asthma exacerbation from the prescribers' point of view. [192] Despite the fact that the type of beta-blockers prescribed herein was cardio-selective, this incidence represents a compelling indication for the use of ivabradine as a

reasonable alternative to EBBB in these circumstances in terms of safety and target HR achievement according to the recommendations of the ESC guidelines. [1]

In the Low-GAI patients, no reason has been appeared to affect prescribing other than the high EF. Among the Low-GAI patients, the prevalence of HFpEF was more likely than in the High-GAI cohort of patients. This may suggest the critical effect of EF level on prescribing practice. Yet, there is no substantial evidence that influences mortality in patients with HFpEF, unlike the robust evidence in HFrEF patients. [1, 57] Patients having HFpEF are often older, with higher levels of comorbidity and are mainly monitored and managed in primary care. [175, 191] However, the current results demonstrated the benefit of High-GAI based management to achieve the guideline-recommended therapeutic goals such as target HR and target BP regardless of the patient's EF. The achievement of these goals is strictly in line with the latest ESC guidelines' recommendations that lead to a significant survival benefit. [1, 193-195]

The utilisation of MRA remains low in this study, similar to the other European reports despite the absence of the guideline-outlined contraindications. [113, 196, 197] The reason for MRA underutilisation is not apparent, but it adds to the fact that managing MRA therapy in outpatient settings is more complicated than managing RASi and EBBB therapies. [113, 196] This can be partly interpreted by the fact that MRA therapy is often associated with worsening renal functions or hyperkalaemia in the presence of a RASi prescription. [113, 196, 197] Another potential cause might be the low prevalence of chronic artery disease in the current population as more MRA evidence has based its use as post-myocardial infarction. [58, 149]

The achievement of the ≥ 50% target dose is suboptimal in the current population, and no patient achieved the 100% target dose of all three guideline-directed medical therapies. The BIOSTAT-

CHF registry conducted in 11 European countries and including 2,500 outpatients showed that a minority of patients were prescribed the target dose of RASi and EBBB. [76] However, there is evidence from observational studies that demonstrate the benefits of target dose prescribing. [1, 46, 86] For instance, in the HF-ACTION study, ambulatory HF patients who achieved EBBB target dose had a 21% reduction in all-cause mortality. [193] Elsewhere, ATLAS and HEAAL clinical trials emphasised the significant benefits of RASi target dose in the reduction of the combined endpoint of mortality or rehospitalisation by 12%, in comparison to lower doses of RASi. [53, 85] Several reasons can contribute to the sub-optimal target dosing in the current setting. Clinical inertia and overestimation of the risk of intolerance of medications uptitration, particularly intolerance of EBBB uptitration are potential barriers to the achievement of the guideline-recommended target doses of HF medications. [185, 198, 199]. For instance, CHAMP-HF registry found that patients did not receive medical therapy titration at any point during their longitudinal follow-up. [200]

According to ESC 2016 guidelines, the figures of the population GAI-3 did not change. As prescribed the optimal guideline-directed therapy at ≥ 50% target dose, only 7.8% patients of the study population who are deemed eligible for ARNi conversion if they remained symptomatic or showed a decrease in EF over six months. All the other patients are not eligible as ARNi prescription requires the precedent achievement of the target doses of all three guideline-direct medical therapies (RASi, EBBB and MRA).

The prescription rate of potentially inappropriate medications herein is higher than that reported in previous reports from Ireland and Australia. [99, 112] These medications may cause harm to HF patients or contradict the effects of guideline-directed medical therapies. [102] Prescription of potentially inappropriate medicines increases the risk of death, acute hospitalisation and

unscheduled outpatient appointment. [99] Unlike a previous Irish study that utilised the PIMHF tool, the present study population are not enrolled in an HF-specific DMP. A disease-specific DMP provides a highly structured multidisciplinary HF care and improves prescribing quality and outcomes. [131, 133] Therefore, exposure to potentially inappropriate medications is less likely in DMP settings.

The rate of potentially inappropriate prescribing in the present study was driven by the prescription of non-dihydropyridine CCB. The multivariable analysis estimated that the prescription of a PIMHF item was associated with chronic respiratory disease and higher HR. [100] The ESC guidelines strongly recommend against the use of non-dihydropyridine CCB in HF, and particularly, in HFrEF. [1, 9] It is possible that prescribers are reluctant to alter any prior prescription as long as the patient is stable and of good quality of life. [198, 200] Alternatively, it may be the case that prescribers are not very familiar with such ESC cautions pointing to a need for ongoing medical education on potentially inappropriate prescribing. [102, 112] For instance, the ESC 2012 and 2016 guidelines recommend the use of ivabradine for achieving the target HR due to its safety profile in HF patients rather than the CCB. [1, 9]

It is also possible that cardiologists are not the primary prescribers to these patients. As ambulatory patients, the general practitioner may be the primary prescriber. [201] Furthermore, given the extent of comorbidities experienced by this patient cohort, this population may also receive prescriptions from other medical specialities such as endocrinologists, pulmonologists, and nephrologists. This diversity of prescribers caring for HF patients may lead to physician's encroachment, deprescribing of a guideline-directed medical therapy or unwitting prescription of potentially inappropriate medicines. [202, 203] For instance, among 2,516 European outpatients, Ouwerkerk and colleagues found that 76% of discontinued MRA occurrences was

not resumed in the outpatient setting. [76] In Ireland, prescribers have limited access to electronic health records, and this could result in prescribing amendments and medication non-persistence. Mockler *et al.* reported that three years post HF diagnosis, 29% of patients are non-persistent to HF medications and that prescriber's decisions rather than patient's actions drove 50% of the non-persistence occurrences. [134]

The drug therapy problems highlighted in this work point to the vital need for clinical pharmacists' inclusion in the hospital outpatient clinic medical team in order to overcome clinical inertia. Implementation of a clinical pharmacy service was found to improve the transition of care and reduced rehospitalisation rates by 30%. [204] Lopez *et al.* showed the significant impact of the clinical pharmacy service to reduce the readmission rate by 35% and to reduce the hospital costs by €600 per patient in 12 months post-discharge. [205] Elsewhere, the clinical pharmacy services optimised the utilisation of the guideline-directed medical therapies up to 15% in a European HF outpatient population. [206] Also, Bhat and colleagues showed the benefits of clinical pharmacists in HF care to overcome clinical inertia in terms of medications uptitration by a significant average optimisation of 20% per medication class. [207]

4.6 Limitations

The study is limited by its small sample size and single centred design that may limit the generalisability of the study results. However, this design contributed to the detailed analysis of some prescribing details in a real-world sample of HF patients. Second, the lack of electronic health records may have limited the comprehensiveness of the data for identifying the documented causes of medication omission or discontinuation.

4.7 Conclusion

In this setting, the majority of HF patients receive guideline-led treatment; however, the proportion of patients reaching the target doses was suboptimal. There is substantial opportunity to improve care and outcomes for ambulatory patients with HF. There is a compelling need for pharmacists to optimise HF prescribing and medication titration in line with the ESC guidelines' recommendations in routine clinical practice. This multidisciplinary care has been shown to help improve the prescription and dosing of guideline-directed therapies to HF patients.

4.8 Acknowledgements

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5 Chapter 5

Guideline–Led Prescribing to the Older Heart Failure Population Resident in Long-Term Care Facilities in Ireland

In Chapter 2, the narrative review discussed the existing HF literature in Ireland. The findings demonstrated that the vulnerable HF patient populations were not included in the published Irish HF literature. Therefore, this chapter aims to (i) identify HF profile in the older HF patients residing in Long-Term Care (LTC) facilities; (ii) examine the level of guideline-led prescribing, and (iii) determine the prevalence of prescribing HF-specific potentially inappropriate medications among LTC HF patients. Evidence from this study will help to identify the divergence of the LTC-based prescribing practice from the ESC guidelines' recommendations and, suggest the potential areas for future HF care improvement in LTC facilities.

5.1 Abstract

5.1.1 Introduction

Heart Failure affects up to 45% of residents in Long-Term (LTC) facilities. This type of patient is often at higher risk of poor HF management and prescription of potentially inappropriate medications.

5.1.2 Aims

To assess the utilisation of HF guideline-directed medical therapies and the prevalence of HF potentially inappropriate prescribing in the Irish LTC facilities.

5.1.3 Methods

This is an observational study of older HF patients in 14 LTC facilities in the greater Cork region of Ireland. Heart failure was documented on patient medical records or identified by the prescription of a loop diuretic. Guideline-led prescribing was assessed using a modified version of the GAI-3 tool. The GAI-3 considers prescription of the loop diuretic, RASi and beta-blocker, and it is adjusted to consider contraindications to therapy. High-GAI was defined as the prescription of ≥ 2 of these agents. Potentially inappropriate prescribing was assessed using the PIMHF tool.

5.1.4 Results

The total number of LTC residents was 732, mean ± SD age 83.9 ± 7.7 years; 30% male. The prevalence of HF was 36.2% (n = 265). Patients with HF were older than those without HF

(84.8 ± 7.4 vs 83.4 ± 7.9 years, *p-value = 0.024*), were more likely to have coronary artery disease (32.5% vs 16.1%, *p-value < 0.001*), and atrial fibrillation (31.3% vs 16.9%, *p-value < 0.001*) but were less likely to have dementia (42.3% vs 49.9%, *p-value = 0.047*). Loop diuretics were prescribed to 87.5% of HF patients (87.5%), RASi to 24.2% and beta-blockers to 22.6%. Mean GAI-3 was 56%. High-GAI was achieved by 54.7% of patients. Patients with High-GAI had a higher comorbidity index (4.8 ± 1.9 vs 3.9 ± 1.8, *p-value < 0.001*) and a greater number of prescribed medications (10.0 ± 3.2 vs 8.4 ± 3.1, *p-value < 0.001*) than those who did not achieve High-GAI. At least one PIMHF item was prescribed to 24.2% of patients. In multivariable analysis, the achievement of High-GAI was associated with a higher comorbidity index score (OR 1.25, 95% CI 1.07 - 1.57) and coronary artery disease (OR 1.78, 95% CI 1.05 – 3.25).

5.1.5 Conclusion

Among older HF patients in this setting, loop diuretic was the primary HF therapy; and there was low utilisation of the other guideline-directed medical therapies. HF-specific potentially inappropriate prescribing is prevalent amongst the LTC population.

5.2 Introduction

Heart Failure affects up to 45% of residents in Long-term Care (LTC) facilities. [208] Long-term Care are a variety of a special facility that provides medically necessary professional services to patients who are not sick enough to need intensive hospital care but are not able to remain at home due to their chronic irreversible or disabling disorders. [209] Heart Failure patients are often vulnerable, and older populations [210, 211] and residents of LTC facilities are often of a similar profile. [212, 213] Older HF patients who require LTC facilities after discharge from hospital face a higher risk of poor HF management and outcomes. [214, 215] The mortality rate among the older HF patients is 22% in the first month after discharge to LTC facilities. [214] Patients hospitalised with HF and discharged to LTC facilities are 50% more likely to be rehospitalised within one month of discharge than those discharged to home. [215]

There are considerable benefits to guideline-led prescribing in reducing the burden of HF complications in older and frail patients, including benefits to patient quality of life and clinical outcomes. [1] Walsh *et al.* demonstrated that 16% of hospitalisations caused by HF exacerbation in the American LTC facilities could have been prevented by the optimal prescribing of the guideline-directed medical therapies. [216] In an octogenarian HF population, appropriate use of HF guideline-directed medical therapies at their recommended target doses showed a better survival rate over five years by 20%. [154] Elsewhere, the prescription of the target dose of HF medications reduced all-cause mortality and hospitalisation by 45% in older ambulatory HF patients in the first year post-discharge. [167]

However, the appropriate prescription of the guideline-directed medical therapies in the older HF patients is complicated. [217] Guideline-led prescribing is frequently limited by multimorbidity, limited physiological reserve, altered drug metabolism and the various side

effects of appropriate and inappropriate multiple medications. [218, 219] Over 50% of the older HF patients have at least three treatment conflicts due to guideline-indicated medicines for a particular comorbid condition with the potential to worsen HF progression or contradict an HF guideline-directed therapy. [99, 220] Polypharmacy is also frequently associated with an increased risk of harmful drug-drug and drug-disease interactions as well as adverse drug effects. [109, 221] In a nationwide study in Australia, almost 60% of an older HF population were prescribed at least one potentially inappropriate medication associated with an increased risk of HF worsening. [99] In another study, non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed to 11% of an older HF population and non-dihydropyridine calcium channel blockers (CCB) to 21%. [186]

5.2.1 Aims

Pharmacotherapy optimisation in LTC represents a challenging public health concern. [218, 219] Literature about optimisation of HF pharmacotherapy and patterns of HF prescribing in LTC facilities is sparse, and there is no data about the target dose achievement of HF guideline-directed medical therapies in this healthcare setting. [156, 215, 218, 222] Therefore, this study has a threefold aim: (i) to measure the level of HF guideline adherence in a sample of Irish LTC facilities; (ii) to determine the prevalence of potentially inappropriate prescribing to HF patients in this setting; and (iii) to identify the clinical factors associated with guideline-led prescribing and potentially inappropriate prescribing in this vulnerable HF population.

5.3 Methods

This study is a secondary data analysis of anonymised data from a previous multi-centre prevalence study performed in 14 LTC facilities in County Cork, Ireland by the Pharmaceutical Care Research Group of University College Cork (UCC), Cork, Ireland. [221] Clinical Research Ethics Committee of the Cork Teaching Hospitals and UCC granted the ethics approval to the original study. The ethics approval was not required for this anonymised secondary data analysis. The study is reported in line with STROBE guidelines. [187]

In the original study, medical records and medication prescription details of all residents in the participating facilities were reviewed at a single time point. [221] Data collection was performed between December 2009 and September 2010. Details of residents' demographics, comorbidities, BP, HR, biochemistry and medications history were extracted from their medical and nursing records. The method of data collection and extraction have been described in detail elsewhere. [221]

The present analysis included all HF patients aged ≥ 65 years identified in the original dataset. Heart Failure was identified through one of two criteria: (i) a previous history of HF diagnosis documented in the resident's medical chart; (ii) the prescription of a loop diuretic to the resident. Due to the high prevalence of undocumented HF diagnosis in LTC facilities, loop diuretics prescription was used as a surrogate marker of the disease identification and severity. [223-225]

Comorbidities were calculated using the Charlson Comorbidity Index adapted to primary care patients. [226] Creatinine clearance was calculated using the Cockcroft – Gault formula. [227]

Chronic renal failure was defined, according to the National Kidney Foundation/ Kidney Disease Outcomes Quality Initiative guidelines, as creatinine clearance ≤ 15 millilitres per minute. [228] Hyperpolypharmacy was defined as the prescription of ≥ 10 regular medications per day. [189] This cut-point was selected due to the high number of medications required for HF management solely in the absence of other comorbidities. [139] The ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2005 were the guidelines referenced throughout this work as they are the guidelines that were in place during the data collection period. [139] The achievement of ≥ 50% and 100% of the target doses of the RASi and beta-blockers was defined as per the ESC 2005 guidelines (Table 5.1). The median and interquartile range (IQR) of furosemide dose equivalents were reported as a measure of HF severity (Table 5.1). [223-225]

The primary outcome of the study was the assessment of HF guideline-led prescribing using the GAI-3. The GAI-3 tool was initially developed by Komajda *et al.* in 2005. [46] The GAI-3 tool is the ratio of the treatment actually prescribed to the treatment that should theoretically have been prescribed of the HF guideline-directed medical therapies: RASi, beta-blocker and MRA. In the current analysis, the GAI-3 was modified so as it considered the prescription of RASi, beta-blocker and loop diuretic owing to the robust evidence-based benefits of loop diuretics in older HF patients. [1, 139] The algorithm used to compute the modified GAI-3 is given in Table 5.1. Based on the individual GAI-3 of each patient, the population was subdivided into High-GAI management, that is the prescription of ≥ 2 GAI medicines or Low-GAI management, that is the prescription of ≤ 1 GAI medicine. [147]

The secondary outcome of the study was the evaluation of potentially inappropriate prescribing using the disease-specific PIMHF tool (Appendix 1) and its effect, if any, on HF guideline-led

prescribing. [112] In this study, only the PIMHF items prescribed regularly were included in the analysis while the *"as required"* items were not included as there was no clear indication of how often the patient received these medications.

5.3.1 Statistical analysis

Quantitative data are presented as mean ± SD or number (%), as appropriate. Continuous data were compared using independent Student's t-test while categorical data by Chi-square test. All tests are two-tailed, and a p-value of < 0.05 was regarded as statistically significant. Univariable and multivariable logistic regression analyses were performed using odds ratios (ORs) with 95% confidence intervals (CI) to determine the clinical factors associated with High-GAI achievement and the factors associated with PIMHF prescribing in the population. Data were analysed using SPSS® version 22.0 for Microsoft® Windows 10.

Table 5.1 Adapted algorithms for computation of the Guideline Adherence Index (GAI-3). [46, 139]

Medication class	Guidelines indications for therapeutic class use	Computation of guideline adherence index (GAI)	Agents	100% Target Dose (mg/day)
Renin-angiotensin system inhibitors (RASi) (ACE inhibitor and angiotensin-II receptor blocker)	1) Prescribe to all Heart Failure patients. 2) Contraindications: (i) bilateral renal artery stenosis; (ii) angioedema; (iii) deteriorating renal functions † or renal failure (creatinine clearance < 15 ml/min).	The guidelines are met if: (i) the patient is prescribed RASi **or** (ii) the patient is not prescribed RASi but has a documented contraindication to RASi.	Ramipril Captopril Enalapril Lisinopril Perindopril arginine Losartan Olmesartan Valsartan	10 150 40 20 5 * 100 20 * 320
Beta-blockers	1) Prescribe to all Heart Failure patients with NYHA class II-IV. 2) Beta-blockers should not be withheld due to old age alone. 3) Contraindications: (i) asthma, (ii) chronic obstructive pulmonary disease, (iii) symptomatic bradycardia † or hypotension, (iv) sick sinus rhythm and AV-block.	The guidelines are met if: (i) the patient is prescribed a beta-blocker **or** (ii) the patient is not prescribed a beta-blocker but has a documented contraindication to beta-blocker therapy.	Atenolol Metoprolol succinate Nebivolol Propranolol	100 * 200 10 160 *
Loop diuretics	1) Prescribe to all Heart Failure patients with any sign/symptoms of congestion, oedema, volume overload or dyspnoea. 2) Loop diuretics should always be prescribed with RASi and beta-blocker.		Furosemide Bumetanide	*40 mg Furosemide equivalent to 1 mg Bumetanide*

The algorithm is adapted from Komajda *et al.* 2005. [46] Agents listed are those agents from each class that were prescribed to one or more patients in the study population. * Dose defined as post-myocardial infarction dose according to the summary of the product characteristics of the medication. [229] † Deteriorating renal functions and symptomatic bradycardia could not be calculated in this dataset as the data were retrospectively analysed at a one-time point. **Abbreviations**: AV-block, atrioventricular block; NYHA, New York Heart Association functional classification; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker).

5.4 Results

5.4.1 Baseline profile and characteristics of Long-Term Care residents

The dataset included 732 residents from 14 LTC facilities. The mean ± SD age of the residents was 83.9 ± 7.7 years, and 70.2% of residents were female (Table 5.2). Chronic kidney disease was the most prevalent comorbidity affecting 552 residents (71.3%) followed by hypertension (n = 349, 47.7%) and dementia (n = 345, 47.1%). The mean ± SD comorbidity index of the residents was 4.0 ± 1.9, and the mean number of medications prescribed per patient was 11.2 ± 4.0 per day.

5.4.2 Identification of Heart Failure patient population

The previous history of HF was documented in the medical charts of 99 patients (13.6%). Loop diuretics were prescribed to a further 166 patients (22.6%) in the absence of a documented HF diagnosis. The comparison between these two cohorts shows small differences between them (Table 5.3). Higher doses of loop diuretics were prescribed to the patients who had no previous history of HF diagnosis in comparison to the doses prescribed to the patients with a documented history of HF, median diuretic daily dose: 220mg (IQR 40 – 420 mg/day) vs 120mg (IQR 30 - 220 mg/day), *p-value < 0.001.*

5.4.3 Comparison of Heart Failure and non-Heart Failure patients

Heart Failure affected 265 LTC residents (36.2%). Heart Failure patients were older than those without HF (84.8 ± 7.4 vs 83.4 ± 7.9, *p-value = 0.024*), more likely to have coronary artery disease (32.5% vs 16.1%, *p-value < 0.001*) and atrial fibrillation (31.3% vs 16.9%, *p-value* <

0.001) but less likely to have dementia (42.3% vs 49.9%, *p-value = 0.047*) and urinary incontinence (32.1 vs 43.7%, *p-value = 0.002*). Patients with HF were prescribed more regular medicines than those without HF (12.7 ± 3.5 vs 10.7 ± 3.7, *p-value < 0.001*), (Table 5.4).

5.4.4 Prescribing to Heart Failure population

In the HF population, RASi was prescribed to 64 patients (24.1%) and beta-blockers to 60 patients (22.6%). Loop diuretics were prescribed to 232 patients (87.5%). Loop diuretics were prescribed as HF monotherapy to 140 patients (52.8%). All three recommended GAI medicines were prescribed to 20 patients (7.7%) while 22 patients (8.3%) were not prescribed any HF-related medications. Mineralocorticoid receptor antagonists were prescribed to 13 patients (4.9%). The different prescribing patterns of HF management are illustrated in Figure 5.1. Achievement of ≥ 50% of the guideline-recommended target doses of RASi occurred in 10.6% of HF patients and beta-blockers in 6.0% of patients. Achievement of 100% target dose occurred in 3.4% and 1.9%, respectively. No patient was prescribed 50% target dose or 100% target dose of both medications.

5.4.5 High-GAI and Low-GAI achievement

Population mean GAI-3 was 55.9%. High-GAI was achieved in 145 patients (54.7%), meaning that 120 of HF patients (45.3%) received one or no GAI medicine (Table 5.5). Patients with High-GAI had higher comorbidity index (4.8 ± 1.9 vs 3.9 ± 1.8, *p-value < 0.001*), and higher prevalence of atrial fibrillation (37.9% vs 23.3%, *p-value < 0.001*), coronary artery disease (41.4% vs 21.7%, *p-value < 0.001*) and asthma/chronic obstructive pulmonary disease (37.2 vs 5.8%, *p-value < 0.001*), than those with Low-GAI. The High-GAI population were more likely to have chronic renal failure (22.1% vs 2.5%, *p-value < 0.001*) and to be prescribed a

greater number of regular daily medications (10.0 ± 3.2 vs 8.4 ± 3.1, *p-value* < *0.001*). A RASi agent was not prescribed to any patient in the Low-GAI cohort.

5.4.6 Potentially inappropriate prescribing

Among residents with HF, 64 (24.2%) were prescribed a PIMHF item, of whom 11 (4.2%) were prescribed ≥ 2 PIMHF items. A COX-2 inhibitor, oral beta-2 agonist, itraconazole or decongestant was not prescribed to any resident. An NSAID was the most frequently prescribed PIMHF item (n = 26, 9.8%), then oral corticosteroids (n = 21, 7.9%). Oral corticosteroids, NSAIDs and pregabalin were the most frequently used PIMHF items among residents prescribed ≥ 2 PIMHF items. There was no difference in the rate of PIMHF prescriptions between High-GAI and Low-GAI HF patients (Table 5.5).

5.4.7 Logistic regression analysis

In a logistic regression analysis, the multivariable associates of High-GAI achievement were higher comorbidity burden (OR 1.25, 95% CI 1.07 - 1.46), coronary artery disease (OR 1.85, 95% CI 1.01 - 3.38) and hyperpolypharmacy (OR 2.04, 95% CI 1.15 – 3.61), (Table 5.6). Prescription of a loop diuretic was negatively associated with PIMHF prescription (OR 0.33, 95% CI 0.15 - 0.73), (Table 5.7).

Table 5.2 Baseline profile of the total population of the 14 Long-Term Care facilities, N = 732 residents. [221]

Variable	Total population characteristics (N = 732)
Age (years)	83.9 ± 7.7
Male	218 (29.8)
Mean arterial blood pressure (mmHg)	90.1 ± 13.4
Heart rate (beats per minute)	74.5 ± 12.5
Creatinine Clearance (millilitre/minute)	53.7 ± 27.9
Hypertension	349 (47.7)
Atrial fibrillation	162 (22.1)
Coronary artery disease	161 (21.9)
Diabetes	110 (15.0)
Chronic renal failure	115 (15.7)
Asthma/Chronic obstructive lung disease	113 (15.4)
Dementia	345 (47.1)
History of falls	349 (47.7)
Cerebrovascular accident/Stroke	211 (28.8)
Urinary incontinence	289 (39.5)
Charlson Comorbidity Index	4.0 ± 1.8
Regular medications	8.3 ± 3.3
Hyperpolypharmacy	163 (22.2)

Table 5.3 Characteristics of Long-Term Care residents with a documented history of Heart Failure and those with prescription of a loop diuretic in absence of documented Heart Failure diagnosis, N = 265 patients.

N = 265 patients	**Documented HF diagnosis** (n = 99)	**Prescription of loop diuretic in absence of documented HF diagnosis** (n = 166)	*p-value*
Clinical profile			
Age (years)	85.5 ± 7.0	84.34 ± 7.6	*0.519*
Male	33 (33.3)	47 (28.3)	*0.372*
MAP (mmHg)	91.5 (12.7)	89.4 (11.8)	*0.767*
Heart rate	73.0 ± 15.0	72.0 ± 18.0	*0.888*
Creatinine Clearance (ml/min)	51.5 ± 25.0	51.8 ± 24.2	*0.145*
Hypertension	43 (43.4)	88 (53.0)	*0.791*
Atrial fibrillation	45 (45.4)	38 (22.9)	*< 0.001*
Coronary artery disease	43 (43.4)	43 (25.9)	*0.021*
Diabetes	17 (17.2)	21 (12.6)	*0.462*
Chronic renal failure	13 (13.1)	22 (13.2)	*0.429*
Asthma / COPD	32 (32.3)	29 (17.5)	*0.526*
Dementia	46 (46.5)	66 (39.8)	*0.518*
History of falls	42 (42.4)	90 (54.2)	*0.618*
CVA / Stroke	29 (29.3)	43 (25.9)	*0.681*
Urinary incontinence	28 (28.3)	57 (34.3)	*0.721*
Number of comorbidities	12.4 ± 4.2	10.8 ± 3.3	*0.031*
Charlson Comorbidity Index	5.3 ± 1.9	3.9 ± 1.8	*0.021*
Medication profile			
RASi	22 (22.2)	42 (25.3)	*0.701*
Beta-blocker	26 (26.6)	34 (20.5)	*0.099*
MRA	8 (8.1)	5 (3.0)	*0.819*
Digoxin	25 (25.2)	12 (7.2)	*< 0.001*
Loop diuretic	66 (66.7)	166 (100)	*< 0.001*
Calcium channel blocker	8 (8.1)	15 (9.0)	*0.310*
Regular medications	12.5 ± 3.6	12.7 ± 3.7	*0.862*
Hyperpolypharmacy	34 (34.3)	53 (31.9)	*0.761*

Comparisons were made between patients with a previous history of Heart Failure diagnosis and patients having a prescription of loop diuretic in absence of documented HF diagnosis. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages. **Abbreviations:** COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HF, heart failure; MAP, mean arterial blood pressure; ml/min., millilitre per minute; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker).

Table 5.4 Characteristics of Long-Term Care residents with Heart Failure and those without Heart Failure, N = 732 patients.

N = 732 patients	Non-HF patients (N = 467)	HF patients [a] (N = 265)	*p-value*
Clinical profile			
Age (years)	83.4 ± 7.9	84.8 ± 7.4	*0.024*
Male	138 (29.6)	80 (30.2)	*0.617*
MAP (mmHg)	90.6 ± 12.0	90.2 ± 12.2	*0.419*
Heart rate (bpm)	75.4 ± 11.1	74.6 ± 12.3	*0.761*
Creatinine Clearance (ml/min)	54.9 ± 29.7	51.7 ± 24.5	*0.537*
Hypertension	218 (46.7)	131 (49.4)	*0.666*
Atrial fibrillation	79 (16.9)	83 (31.3)	*<0.001*
Coronary artery disease	75 (16.1)	86 (32.5)	*<0.001*
Diabetes	72 (15.4)	38 (14.3)	*0.671*
Chronic renal failure	80 (17.1)	35 (13.2)	*0.761*
Asthma / COPD	52 (11.1)	61 (23.0)	*0.021*
Dementia	233 (49.9)	112 (42.3)	*0.047*
History of falls	217 (46.5)	132 (49.8)	*0.871*
CVA / Stroke	139 (29.8)	72 (27.2)	*0.691*
Urinary incontinence	204 (43.7)	85 (32.1)	*0.002*
Number of comorbidities	10.6 ± 3.4	11.6 ± 3.5	*0.035*
Charlson Comorbidity Index	3.8 ± 1.6	4.4 ± 1.9	*0.029*
Medications profile			
RASi	71 (15.2)	64 (24.2)	*0.031*
Beta-blocker	71 (15.2)	60 (22.6)	*0.041*
MRA	7 (1.5)	13 (4.9)	*0.418*
Digoxin	31 (6.6)	37 (14.0)	*0.024*
Loop diuretics	0 (0.0)	232 (87.5)	*< 0.001*
Calcium channel blocker	42 (9.0)	23 (8.7)	*0.318*
Regular medications	7.6 ± 3.2	9.27 ± 3.2	*0.041*
Hyperpolypharmacy	76 (16.3)	87 (32.8)	*<0.001*

a: Heart Failure defined as patients with Heart Failure diagnosis or patients prescribed loop diuretic, *highlighted in grey colour*. Comparisons were made between Heart Failure patients and non-Heart Failure patients. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages**.**

Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; HF, heart failure MAP, mean arterial blood pressure; RASi, renin-angiotensin system inhibitor (ACE inhibitor and angiotensin-II receptor blocker).

Table 5.5 Characteristics of Heart Failure patients receiving High-GAI and Low-GAI management, N = 265 patients.

N = 265 patients	High-GAI (n = 145)	Low-GAI (n = 120)	*p-value*
Clinical profile			
Age (years)	84.4 ± 7.1	85.2 ± 7.6	*0.351*
Male	46 (31.7)	34 (28.3)	*0.852*
MAP (mmHg)	89.5 ± 12.6	91.1 ± 11.7	*0.671*
Heart rate (bpm)	73.3 ± 13.3	76.1 ± 12.8	*0.787*
Hypertension	79 (54.5)	52 (43.3)	*0.050*
Atrial fibrillation	55 (37.9)	28 (23.3)	*< 0.001*
Coronary artery disease	60 (41.4)	26 (21.7)	*< 0.001*
Diabetes	22 (15.2)	16 (13.3)	*0.887*
Chronic renal failure	32 (22.1)	3 (2.5)	*< 0.001*
Asthma/COPD	54 (37.2)	7 (5.8)	*< 0.001*
Dementia	56 (38.6)	56 (46.7)	*0.562*
History of falls	67 (46.2)	65 (54.2)	*0.251*
Number of comorbidities	12 ± 3.4	11.2 ± 3.5	*0.371*
Charlson comorbidity index	4.8 ± 1.9	3.9 ± 1.8	*<0.001*
Medication profile			
Regular medications	10.0 ± 3.2	8.4 ± 3.1	*<0.001*
Hyperpolypharmacy	59 (40.7)	28 (23.3)	*< 0.001*
Potentially Inappropriate Medicines in Heart Failure			
NSAID	9 (6.2)	17 (14.2)	*0.06*
Oral corticosteroid	14 (9.7)	7 (5.8)	*0.912*
Pregabalin	9 (6.2)	5 (4.2)	*0.816*
Metformin in poor renal function †	8 (5.5)	1 (0.8)	*0.819*
Non-dihydropyridine CCB	2 (1.4)	3 (2.5)	*0.738*
Thiazolidinedione (-glitazones)	1 (0.7)	0.0	*0.981*

Comparisons were made between Heart Failure patients with High-GAI and those with Low-GAI management. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages. * indicates a statistically significant *p-value* < *0.05*. † poor renal function is defined as creatinine clearance < 50 millilitres/minute. **Abbreviations**: bpm, beats per minute; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; GAI, guideline adherence index; HF, heart failure; MAP: mean arterial blood pressure; NSAID, non-steroidal anti-inflammatory drugs.

Table 5.6 Univariable and multivariable logistic regression of High-GAI achievement among residents with Heart Failure, N = 265 patients.

Variable	Univariable analysis Odds ratio (95% Confidence Interval)	Multivariable analysis Odds ratio (95% Confidence Interval)
Age (years)	0.98 (0.951 – 1.010)	0.978 (0.948 - 1.023)
Male	1.17 (0.691 – 1.990)	1.023 (0.555 - 1.888)
Charlson comorbidity index	1.31 (1.141 – 1.515)	1.249 (1.074 - 1.457)
Atrial fibrillation	2.00 (1.170 – 3.450)	1.737 (0 .955 - 3.006)
Coronary artery disease	2.55 (1.479 – 4.405)	1.784 (1.059 - 3.250)
Dementia	0.719 (0.446 – 1.17)	-
Hyperpolypharmacy	2.254 (1.317 – 3.858)	2.039 (1.150 - 3.614)
PIMHF item prescribed	0.919 (0.523 – 1.615)	-

The multivariable logistic model of High-GAI achievement: *Nagelkerke's R^2 = 0.159; percentage of correct estimation = 66.6%*. **Abbreviations**: PIMHF, potentially inappropriate medicines in heart failure.

Table 5.7 Univariable and multivariable logistic regression of the use of Potentially Inappropriate Medicines in Heart Failure among residents with Heart Failure, N = 265 patients.

Variable	Univariable analysis Odds ratio (95% Confidence Interval)	Multivariable analysis Odds ratio (95% Confidence Interval)
Age (years)	0.961 (0.923 - 1.012)	0.966 (0. 927 - 1.021)
Male	1.29 (0.713 - 2.352)	1.155 (0.591 - 2.174)
Dementia	0.991 (0.566 - 1.761)	-
Documented Heart Failure diagnosis	0.834 (0.469 – 1.482)	-
Hyperpolypharmacy	1.570 (0.877 - 2.812)	-
Loop diuretic	0.373 (0.179 - 0.792)	0.355 (0.165- 0. 765)

The multivariable logistic model of PIMHF prescription: *Nagelkerke's R^2 = 0.55; percentage of correct estimation = 77.5%.* **Abbreviations**: PIMHF, potentially inappropriate medicines in heart failure.

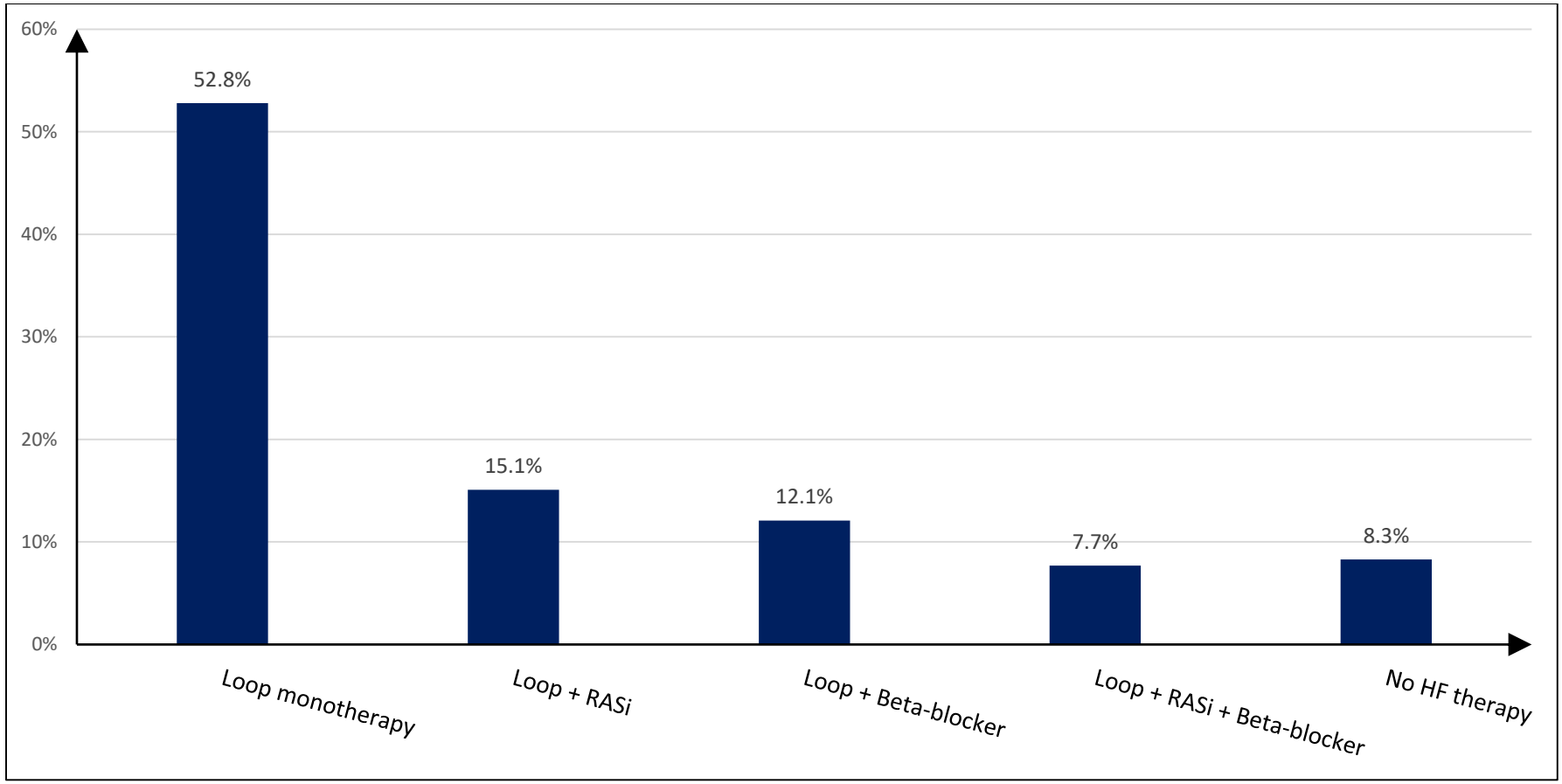


Figure 5.1 The most frequent prescribing patterns of Heart Failure medications, N = 265 patients.

Abbreviations: HF, heart failure; loop, loop diuretic; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker)

5.5 Discussion

Prescribing of medicines is a fundamental element of HF care in all healthcare settings. [1] The current study represents a unique assessment of the prescribing of HF guideline-directed medical therapies and the patterns of appropriate and potentially inappropriate HF prescribing practices in LTC facilities. This study is the first application of the GAI-3 and PIMHF prescribing review tools in an LTC context. The results illustrate the considerable sub-optimal utilisation of guideline-directed medical therapies in this population of older HF patients and that one in four of these HF patients was prescribed at least one medicine that is potentially harmful in HF.

Accurate HF diagnosis is challenging in older patients and particularly among LTC residents for many reasons including frailty, dementia, multimorbidity, immobility, and polypharmacy. [114, 219, 223, 224] This means that many HF cases are undiagnosed or undetected as the HF manifestations may be misinterpreted as ageing-related or as symptoms of other illnesses. [213, 218, 223, 224] Hancock and colleagues found that HF diagnosis is missed in 50% of LTC residents with previously recorded HF diagnosis in their hospital charts. [224] A study by Heckman et *al.* of 450 HF patient residents in LTC showed that previous history of HF (OR 13.66, 95% CI 6.61 – 28.24) and prescription of a loop diuretic (OR 2.11, 95% CI 1.12 – 3.98) are the strongest diagnostic predictors of HF in LTC facilities. [223] The use of loop diuretic as a surrogate marker of HF in this study population is supported by the fact that prescription of loop diuretics has been used to aid diagnosis in the older HF patients in clinical trials such as *The Perindopril in Elderly People with Chronic Heart Failure* (PEP-CHF) study and the *Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure* (TIME-CHF). Furthermore, the present results showed the very high median dose of loop diuretics that was prescribed to the cohort of patients that had not a documented HF diagnosis in comparison to

the dose prescribed to the cohort of patients having the diagnosis documented in their charts. [211, 230] Other HF surrogate markers such as natriuretic peptides have been used to identify HF in the older LTC residents. [211] The ambiguity surrounding the diagnosis of HF may adversely impact guideline-led prescribing practice, medication choice and dosing offered to the HF population in LTC facilities. [223, 224]

The impact of this uncertain diagnosis could be reflected in the utilisation rates and dosing of the recommended HF medications. The prescription rates of RASi (24.1%) and beta-blockers (22.6%) in the present study were significantly lower than those outlined in the *Geriatric Outcomes and Longitudinal Decline in Heart Failure* (GOLD-HF) study where RASi was prescribed to 60% of HF patients and beta-blockers to 50% of patients. In a study of American Medicare/Medicaid certified nursing homes by Li *et al*., RASi was prescribed to 56% of residents and beta-blockers to 54%. [218, 219]

The older age represents a considerable barrier to guideline-led prescribing and the uptitration of the medications in LTC facilities. [218, 224] In the current HF population, the 100% target dose was achieved in less than 5% of patients only. Li and colleagues justified the prescription of RASi and beta-blocker to fewer than 60% of otherwise eligible HFrEF patients by the fact of the patients older age. [218] Barywani and colleagues found that among ambulatory octogenarian patients, 53% achieved the guideline-recommended target doses of RASi, and just 21% achieved the beta-blocker target dose. [154] The older HF patients and particularly those in LTC represent a gap in the HF evidence as they are frequently excluded from the clinical trials. [109] Furthermore, as medication side effects can be more pronounced in older patients, those who prescribe to LTC residents may be reluctant to start, resume or uptitrate a guideline-directed medication. [1, 185, 231]

However, the regression model estimated an opposite effect of coronary artery disease and the comorbidity burden on the achievement of High-GAI based management. The adjusted model estimated coronary artery disease (OR 1.84, 95% CI 1.01 – 3.38) as a positive associate of HF guideline-led prescribing. Similarly, Li *et al.* study in the USA showed the positive impact of comorbid cardiovascular conditions or risk factors on the prescription of RASi and beta-blockers in LTC residents. [218] Both Li *et al.* and the current study identified a positive relationship between comorbidity burden and the achievement of High-GAI based management despite using different methods of comorbidity calculation. [218]

Overall, adherence to guideline-led prescribing in the current population is moderate despite the adjustment for patients' contraindications to therapies. In some instances, this suboptimal use of HF medications might be an appropriate strategy for the older multimorbid HF patients. TIME-CHF trial did not demonstrate any mortality or hospitalisation benefit related to the intensification of medications in these vulnerable patients, but this intensification strategy was associated with more serious adverse drug reactions in older patients in comparison to the younger HF patients. [211, 232]

The current study showed that one-quarter of patients were prescribed at least one potentially inappropriate medicine. This is in line with international reports that potentially inappropriate prescribing is highly prevalent in LTC facilities, ranging from 12% in one report to 70% in another. [221, 233] Despite the different specificity of PIMHF compared to other explicit tools, the current results are confirmatory to the findings of a previous analysis of the current population. [221] That study applied the STOPP/START criteria to all 732 residents of the current LTC facilities and found a 70% prevalence of potentially inappropriate prescribing. [221]

There is clear evidence that the use of certain medications is harmful or contraindicated in HF patients as they may cause or exacerbate congestion or have a detrimental inotropic effect. [102] The PIMHF prescribing review tool may be of benefit in identifying opportunities to improve prescribing quality in HF patients residing in LTC. [112]

The drug therapy problems identified in this work represent a unique opportunity for the inclusion of clinical pharmacists into the multidisciplinary healthcare teams of LTC facilities. Implementation of a clinical pharmacy service improved the transition of care and reduced rehospitalisation rates by up to 30% among patients of high cardiovascular risk. [204] However, there is a striking lack of HF-specific studies concerned about the role of clinical pharmacists in LTC facilities. There was an uncontrolled before-after study performed in two Belgian nursing homes over 100 patients and published in 2010. In these two nursing homes, an educational intervention led by a clinical pharmacist decreased the rate of medication errors by more than 50% in three months only. [234]

5.6 Limitations

The one-point data collection limited the opportunity to study medications modifications over time. Also, the uncertain diagnosis of HF in 166 residents might have affected the quality of prescribing. Prescription rates were reported assuming these would be the same as utilisation rates, as the residents' medication administration is monitored by nursing staff at the LTC facilities. Similar to the Canadian GOLD-HF study, the study data was collected a number of years before its analysis, however, given the paucity of data on prescribing to patients in LTC settings and the challenges of collecting such data the results of this work remain relevant. [219]

5.7 Conclusion

Adherence to guideline-led prescribing is moderate in these LTC facilities. Prescription rates of potentially inappropriate medications are high among older HF patients. However, optimising medications in this population is hampered by difficulties in confirming HF diagnosis.

5.8 Acknowledgements

The research team would like to acknowledge Mr David O'Sullivan and previous authors of the original study.

6 Chapter 6

Guideline-Led Prescribing to Heart Failure Patients at Discharge from an Egyptian Critical Care Unit: The Impact of a Clinical Pharmacy Service

According to the literature review of published HF studies in Egypt (Chapter 2), the number of HF clinical care studies is scarce. Also, the review demonstrated that some healthcare settings were not included in any of the published studies. Therefore, the aim of this chapter is to study HF guideline-led prescribing towards recently stabilised HF patients at the discharge point from the critical care setting. Evidence from this study may help to identify the potential contribution of a clinical pharmacist in routine practice.

6.1 Abstract

6.1.1 Introduction

Discharge prescriptions for HF patients may not adhere to the recommendations of the clinical practice guidelines. Clinical pharmacists are uniquely positioned to optimise HF prescribing and uptitrate the guideline-directed medical therapies.

6.1.2 Aims

To assess guideline-led prescribing to HF patients at discharge from an Egyptian critical care setting and the impact of the introduction of a clinical pharmacy service.

6.1.3 Methods

A retrospective observational study of HF patients discharged from a critical care unit (CCU) between 2013 and 2017. The GAI-3 was used to assess guideline-led prescribing. High-GAI was the prescribing of ≥ 2 GAI medicines. A clinical pharmacy service was introduced to the CCU on January 1st, 2016.

6.1.4 Results

The study included 284 HF patients, mean ± SD 66.7 ± 11.5 years, 53.2% male. At discharge, loop diuretic was the most frequently prescribed HF medication (n = 242, 85.2%); followed by MRA (n = 156, 54.9%); RASi (n = 146, 51.4%); and beta-blockers (n = 85, 29.9%). Population GAI-3 was 45.5%; however, when adjusted for prescription of ≥ 50% target dose this decreased to 24.3%. High-GAI was prescribed to 136 patients (47.9%). These patients were younger (62.6

vs 70.5 years, *p-value* < *0.001*); less affected by kidney disease (22.1% vs 33.8%, *p-value* = *0.028*) and had fewer comorbidities (4.9 ± 2.3 vs 5.6 ± 2.5, *p-value* = *0.017*) than those without High-GAI. Prescription of beta-blocker increased (24.1% vs 38.6%, *p-value* < *0.001*) and digoxin utilisation decreased (34.7% vs 23.7%, *p-value* < *0.049*) after the introduction of the clinical pharmacy service.

6.1.5 Conclusion

Contraindications, older age and kidney function adversely affected guideline-led prescribing in this critically-ill population. Clinical pharmacists may have a role in optimising guideline-led prescribing in the CCU.

6.2 Introduction

Pharmacotherapy is a core component of HF management as it improves symptoms and prevents worsening of the disease. [1, 21, 48] Guideline-led prescribing is strongly associated with improved survival, prognosis, and quality of life in HF. [1, 21, 48, 76] The guidelines strongly recommend, and the optimal patient outcomes are achieved with the appropriate prescription of the target doses of HF guideline-directed medical therapies. [41, 84] In the BIOSTAT-CHF and QUALIFY studies, the optimisation of HF guideline-directed medical therapies and the prescription of ≥ 50% of target doses demonstrated short and long-term benefits in patient survival and rehospitalisation outcomes. [48, 76]

Hospitalisation is a significant opportunity to implement guideline-directed medical therapies for chronic HF in a monitored setting. A meta-analysis studying the effects of EBBB demonstrated that discontinuation of EBBB in patients hospitalised with acute HF was associated with significantly increased in-hospital mortality, short-term mortality and short-term rehospitalisation. [42] Therefore, in-hospital initiation or resumption of guideline-directed medical therapies is one of the significant predictors of optimal long-term use of therapies and consequently, better clinical outcomes. [235] However, studies evaluating prescribing at discharge show that discharge therapeutic plans for HF patients are often not adherent to the guidelines. [235, 236] In one long-term registry, discharge prescription rates of HF guideline-directed medical therapies were lower than 75%. [236] Elsewhere, Gilstrap and colleagues identified some reasons for the considerable omission of HF guideline-directed medical therapies during hospitalisation or at discharge despite their survival benefits. [146, 237] For instance, reduced kidney functions and hypotension represent substantial barriers to the prescription of the full list of HF guideline-directed medical therapies.

Mainly, little is known about the quality of HF prescribing at discharge from critical care units. The critically-ill HF population represents a challenge for prescribers as these patients are often older, suffering from multiple severe comorbidities, prescribed appropriate and inappropriate polypharmacy and more likely to experience contraindications to therapies. [21, 236, 238] Therefore, discharge prescribing may not be optimised in this population. [21, 236]

The clinical pharmacist is uniquely positioned to address such drug therapy problems in order to optimise HF care and improve clinical outcomes. [239] Implementation of clinical pharmacy services can improve the transition of care and reduce rehospitalisation rates by up to 30%. [204] The inclusion of clinical pharmacists in HF care teams has been shown to optimise guideline-led prescribing during and after hospitalisation. [206] However, there are no reports on clinical pharmacist activities in HF in the MENA settings [16, 206] and little is known about guideline-led prescribing towards recently stabilised HF patients at discharge from critical care units in the MENA region. [16]

The Egyptian Long-Term Registry is an HF registry that represents a comprehensive dataset from cardiology wards and settings throughout the country. However, there is no data about HF care in non-cardiology settings or the effect of clinical pharmacists in HF management. [16, 143]

6.2.1 Aims

Therefore, this study aimed to assess guideline-led prescribing to HF patients at discharge from a critical care setting and to assess the effect, if any, of including a clinical pharmacist in this setting.

6.3 Methods

This is a retrospective observational study of HF patients hospitalised in the Critical Care Unit, (CCU) of Cairo University Hospitals, Egypt, between January 1st, 2013 and December 31st, 2017. The ethics approval was granted by the Research and Ethics Committee of Future University in Egypt, Cairo, Egypt *(registration number REC-FPSPI-9/56),* (Appendix 6). Permission to conduct the research was granted by the Management Board of Critical Care Medicine Department of Cairo University, Egypt. The study is reported according to STROBE guidelines. [187]

Patients were included if they were ≥ 18 years on the date of admission, had a diagnosis of HF, had an electronic record of discharge medications and were discharged from the CCU during the study period. The diagnosis and type of HF were based on data recorded in the patient's electronic medical record. Heart Failure with reduced ejection fraction was defined as an EF < 50% while HFpEF was defined as an EF ≥ 50%. [9] Data accessed in the patient's electronic medical record included age, gender, admission date, discharge date, presenting complaint; comorbidities, laboratory and medical investigations. The following information on discharge medications was also accessed in the electronic medical records: drug name, dose and frequency. As this population is prescribed a high number of medications, hyperpolypharmacy, that is the prescription of ≥10 regular daily medications, was calculated. [189]

The ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 are the guidelines referenced throughout this work as they are the guidelines that were in use in Egypt for most of the study timeframe. [9] Guideline-led prescribing was assessed using the GAI-3 [46], the adjusted GAI-3 [176] and the GAI-based target dose. [179] The GAI-3 was calculated as the proportion of each of the following medications prescribed for each patient:

RASi (ACE inhibitor or ARB), EBBB MRA. [9, 46] The adjusted GAI-3 took into account patient's contraindications to these therapies (Table 6.1). [9, 147, 176] The GAI-based target dose considered the prescription of ≥ 50% of the recommended target dose of each of the pharmacological substance class as adherence to the guidelines (Table 6.1). [9, 179] The GAI-5 was calculated using five medication classes: the GAI medicines plus digoxin and loop diuretics. [9, 46] The study population was then subdivided into those with High-GAI based management; that is the prescription of ≥ 2 of the GAI medicines and those with Low-GAI based management; the prescription of ≤ 1 GAI medicine. [147] Potentially inappropriate prescribing was evaluated using the PIMHF tool, an HF-specific list that includes 11 medicines or medicine classes that are cautioned or contraindicated in HF patients (Appendix 1). [112]

6.3.1 Clinical Pharmacy service in the Critical Care Unit

Clinical pharmacy service was introduced in the CCU from January 1st, 2016 onwards. The clinical pharmacy team was composed of five clinical pharmacists, each with more than four years of clinical experience and a senior pharmacist director with greater than 10 years clinical experience and holds a PhD in Clinical Pharmacy. The clinical pharmacists (i) participate in the daily ward round to provide prescribing recommendations; (ii) perform medication review and medication reconciliation to identify drug-related problems; and (iii) provide a drug information service for prescribers.

6.3.2 Statistical analysis

Comparisons between (i) patients with High-GAI and Low-GAI based management and (ii) patients receiving care before and after the introduction of the clinical pharmacy service were conducted using independent Student's t-test for continuous data and *Chi*-square or Fisher's

exact test for categorical data. All tests were two-tailed, and a *p-value of* < 0.05 was regarded as statistically significant.

Univariable logistic regression analysis was performed and a multivariable logistic regression model developed in order to determine the clinical factors associated with High-GAI achievement. The multivariable logistic regression model included the variables that were considered clinically relevant and variables where there was a significant difference in the comparison between High-GAI and Low-GAI populations. Therefore, the multivariable model adjusted for age and sex included the number of comorbidities, HF type, blood urea nitrogen > 20 mg/dl, serum creatinine > 2.5 mg/dl, and prescription of ivabradine. The odds ratios (OR) and 95% confidence intervals (CI) of the adjusted multivariable analysis were reported. Data were analysed using SPSS® version 22.0 for Microsoft Windows 10.

Table 6.1 Guideline-directed medical therapies, their contraindications, and target doses as described in the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012. [9]

Medication class	Contraindications	Agents	100% Target Daily Dose
Renin-angiotensin system inhibitors (ACE inhibitor / Angiotensin-II receptor blocker)	• History of angioedema • Known bilateral renal artery stenosis • Pregnancy/risk of pregnancy	Captopril Enalapril Lisinopril Ramipril Candesartan Losartan Valsartan	150 mg 20 mg 20 mg 10 mg 32 mg 150 mg 320 mg
Evidence-based beta-blockers	• Second- or third-degree AV block • Asthma: *COPD is not a contra-indication*	Bisoprolol Carvedilol Nebivolol	10 mg 50 mg 10 mg
Mineralocorticoid receptor antagonists	• Eplerenone use with strong cytochromes inhibitors	Spironolactone Eplerenone	50 mg 50 mg
Digoxin	-		-
Loop diuretics	-		**Usual daily dose**
		Furosemide	≤ 240 mg
		Bumetanide	≤ 5 mg
		Torsemide	≤ 20 mg

Agents listed are those agents from each class that were prescribed to one or more patients in the study population. **Abbreviations:** ACE, angiotensin-converting enzyme; AV-block, atrioventricular block; COPD, chronic obstructive pulmonary disease.

6.4 Results

6.4.1 Baseline profile and characteristics of Heart Failure patients

Data were available for 284 patients. The mean ± SD age of patients was 66.7 ± 11.5 years, and 53.2% were male. Ejection fraction was available for 220 patients, and the mean ± SD EF was 45.1% ± 16.7%. Heart Failure with reduced ejection fraction affected 138 patients (62.7%). Coronary artery disease was the HF aetiology in 132 patients (46.5%), and the acute coronary syndrome was the main presenting complaint in 81 patients (28.5%). The mean number of comorbidities was 5.2 ± 2.4 with hypertension (n = 140, 49.3%), diabetes (n = 130, 45.8%) and atrial fibrillation (n = 109, 38.4%) as the most frequently occurring comorbidities (Table 6.2).

6.4.2 Prescribing to Heart Failure population

At discharge, the mean number of daily medications was 9.1 ± 2.5 (Table 6.2). Fourteen patients (4.9%) were not prescribed any HF medications. Prescription rates for the three GAI medicines were RASi (n = 146, 51.4% patients); EBBB (n = 85, 29.9% patients); and MRA (n = 156, 54.9% patients). Monotherapy was prescribed to 53 patients (18.7%) of whom, 45 (15.8%) were prescribed a loop diuretic as the single HF medication. A combination of two GAI medicines was prescribed to 94 (33.1%) patients, and all three medicines were prescribed to 42 (14.8%) patients. Prescription of ≥ 50% of the guideline-recommended target doses of RASi, EBBB and MRA was achieved in 40 (14.1%), 21 (7.4%) and 145 (51.5%) patients, respectively (Figure 6.1). The most frequently prescribed HF medication was loop diuretics (242 patients, 85.2%), with 43 (15.2%) patients prescribed more than one loop diuretic at discharge. The usual daily dose of loop diuretics was exceeded in 39 (13.7%) patients.

The contraindications to the guideline-directed medical therapies, as outlined in the guidelines, are described in Table 6.1. No patient experienced a contraindication to RASi or MRA. At least one contraindication to EBBB therapy was present in 70 (24.6%) patients, 23 (8.1%) having a second or third-degree AV-block and 47 (16.5%) having asthma. Of these patients, 49 (17.2%) were not prescribed an EBBB at discharge.

Population mean GAI-3 was 45.5%, and adjusted GAI-3 was 51.3%. GAI-3 target dose was 24.3%. Population mean GAI-5 was 50.3%. There were significant differences between HFrEF and HFpEF patients in GAI-3 (56.6% vs 26.3%, *p-value* < *0.001*); adjusted GAI-3 (62.4% vs 33.8%, *p-value* < *0.001*) and GAI-5 (60.0% vs 34.4%, *p-value* < *0.001*). PIMHF items were prescribed to 51 (18.1%) patients (Table 6.2).

6.4.3 High-GAI and Low-GAI achievement

High-GAI based management was achieved in 136 patients (47.9%). These High-GAI patients had lower EF (37.9% ± 13.8% vs 51.9% ± 16.4%, *p-value* < *0.001*); were younger (62.6 ± 10.7 vs 70.5 ± 11 years, *p-value* < *0.001*); were more likely to be male (65.4% vs 41.9%, *p-value* < *0.001*); had fewer comorbidities (4.9 ± 2.3 vs 5.6 ± 2.5, *p-value* = *0.017*); and were less likely to have chronic kidney disease (22.1% vs 33.8%, *p-value* = *0.028*) than those patients with Low-GAI. Also, the prescription of recommended target doses of RASi, EBBB and MRA were significantly higher in the High-GAI cohort than the Low-GAI cohort (Figure 6.1).

6.4.4 Clinical Pharmacy contribution

There was no statistical difference between HF patients before (n = 170) and after (n =114) the introduction of clinical pharmacy service in terms of demographic characteristics or

comorbidities. Medications prescribed in the period before and after the introduction of the service are described in Table 6.3. The prescription of EBBB increased significantly from 24.1% before the clinical pharmacy service to 38.6% post the implementation of the service (*p-value < 0.001*) while the prescription of digoxin decreased significantly during the same period (34.7% vs 23.7%, *p-value = 0.049)*. Prescribing of pregabalin, a PIMHF item, increased after introduction of clinical pharmacy (0.6% vs 7.9%, *p-value < 0.001*).

6.4.5 Logistic regression analysis

In the multivariable logistic regression analysis, the clinical factors associated with High-GAI were age (OR 0.96, 95% CI 0.92 - 0.98), serum creatinine > 2.5 mg/dl (OR 0.31, 95% CI 0.09 – 0.98) and HFrEF (OR 5.50, 95% CI 2.66 – 11.55). The model estimation correctness was 72.7 % and Nagelkerke's $R^2 = 0.36$.

Table 6.2 Baseline characteristics and medications profile of the total population, patients prescribed High-GAI and patients prescribed Low-GAI, N = 284 patients.

N = 284 patients	**Total Population (n = 284)**	**High-GAI (n = 136)**	**Low-GAI (n = 148)**	***p-value***
Clinical profile				
Age (years)	66.7 ± 11.5	62.6 ± 10.7	70.5 ± 11	*<0.001*
Male	151 (53.2)	89 (65.4)	62 (41.9)	*<0.001*
MAP (mmHg)	94.9 ± 17.6	93.3 ± 19	96.3 ± 16.2	*0.436*
Heart rate (bpm)	86.2 ± 22.0	87.9 ± 21.6	84.6 ± 22.3	*0.701*
Ejection Fraction (%)[†]	45.1 ± 16.7	37.9 ± 13.8	51.9 ± 16.4	*< 0.001*
HFrEF[†]	138 (62.7)	89 (83.2)	49 (43.4)	*< 0.001*
Hypertension	140 (49.3)	69 (50.7)	71 (48.0)	*0.313*
Atrial fibrillation	109 (38.4)	48 (35.3)	61 (41.2)	*0.541*
Coronary artery disease	132 (46.5)	69 (50.7)	63 (42.6)	*0.376*
Diabetes	130 (45.8)	60 (44.1)	70 (47.3)	*0.132*
Chronic kidney disease	80 (28.2)	30 (22.1)	50 (33.8)	*0.028*
Asthma/COPD	64 (22.5)	34 (25.0)	30 (20.3)	*0.812*
Number of comorbidities	5.2 ± 2.4	4.9 ± 2.3	5.6 ± 2.5	*0.017*
Clinical Status at Discharge				
Low blood pressure (*<90/60 mmHg)*	9 (3.5)	8 (6.7)	1 (0.7)	*0.011*
High blood pressure *(>140/90 mmHg)*	88 (34.6)	34 (28.6)	54 (40.0)	*0.214*
Heart rate ≤ 70 bpm	107 (37.7)	46 (33.8)	61 (41.2)	*0.333*
Heart rate ≥ 100 bpm	57 (20.1)	28 (25.5)	29 (24.0)	*0.412*
Hyperkalaemia (K^+ > 5.0 mg/dl)	9 (3.2)	3 (2.2)	6 (4.1)	*0.877*
High blood urea nitrogen (> 20 mg/dl)	153 (53.9)	63 (46.3)	90 (60.8)	*< 0.01*
High serum creatinine (> 2.5 mg/dl)	31 (10.9)	7 (5.1)	24 (16.2)	*< 0.01*
Length of stay (days)	9.8 ± 6.9	9.3 ± 7.4	10.3 ± 6.5	*0.049*

Table 6.2 Baseline characteristics and medications profile of the total population, patients prescribed High-GAI and patients prescribed Low-GAI, N = 284 patients, *Cont'd.*

	Total Population (n = 284)	High-GAI (n = 136)	Low-GAI (n = 148)	*p-value*
Discharge Medications Profile				
RASi	146 (51.4)	125 (91.9)	21 (14.2)	*< 0.001*
EBBB	85 (29.9%)	67 (49.3)	18 (12.2%)	*< 0.001*
MRA	156 (54.9)	122 (89.7)	34 (23.0)	*< 0.001*
Digoxin	86 (30.3)	48 (35.3)	38 (25.7)	*0.501*
Loop Diuretics	242 (85.2)	120 (88.2)	122 (82.4)	*0.423*
Ivabradine	31 (10.9)	21 (15.2)	10 (6.8)	*0.020*
PIMHF items prescribed	51 (18.1)	19 (14.0)	32 (21.6)	*0.312*
Regular medications	9.1 ± 2.5	9.3 ± 2.3	8.9 ± 2.6	*0.545*
Hyperpolypharmacy	121 (43.7)	59 (43.4)	62 (41.9)	*0.065*
Device-based therapy ≀	38 (13.4)	19 (14.0)	19 (12.8)	*0.435*
Major Prescribing Patterns at Discharge				
Loop diuretic as monotherapy	45 (15.8)	-	45 (30.4)	-
RASi + Beta blocker	56 (19.7)	56 (41.7)	-	-
RASi + MRA	110 (38.7)	110 (80.9)	-	-
Loop diuretic + RASi	123 (43.3)	108 (79.4)	15 (10.1)	*< 0.01*
Loop diuretic + MRA	146 (51.4)	114 (83.8)	32 (21.6)	*< 0.01*
Loop diuretic + MRA + Digoxin	54 (19.1)	43 (31.6)	11 (7.4)	*0.021*
Loop diuretic + RASi + MRA	102 (35.9)	102 (75.0)	-	-

Comparisons were made between Heart Failure patients with High-GAI and Low-GAI. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation. †Ejection fraction available for 220 patients. ≀ Device-based therapy: implantable cardiac defibrillator, cardiac resynchronisation therapy or left ventricular assistance device.
Abbreviations: COPD, chronic obstructive pulmonary disease; EBBB, evidence-based beta-blocker; GAI, Guideline Adherence Index; HFrEF, heart failure with reduced ejection fraction; K^+, serum potassium; MAP, mean arterial blood pressure; MRA, mineralocorticoid receptor antagonist; PIMHF, potentially inappropriate medicines in heart failure; RASi, renin-angiotensin system inhibitor (ACE inhibitor or angiotensin-II receptor blocker).

Table 6.3 Prescribing of Heart Failure medications before and after implementation of clinical pharmacy service, N = 284 patients.

N = 284 patients	Before Clinical Pharmacy (2013-2015) (n = 170)	After Clinical Pharmacy (2016-2017) (n = 114)	*P-value*
Discharge Medications Profile			
RASi	91 (53.5)	55 (48.2)	*0.345*
RASi ≥ 50% Target dose	25 (14.7)	15 (13.2)	*0.456*
EBBB	41 (24.1)	44 (38.6)	*<0.001*
EBBB ≥ 50% Target dose	9 (5.3)	12 (10.5)	*0.218*
MRA	99 (58.2)	57 (50.0)	*0.546*
MRA ≥ 50% Target dose	93 (54.7)	52 (45.6)	*0.617*
Digoxin	59 (34.7)	27 (23.7)	*0.049*
Loop diuretic	149 (87.6)	93 (81.6)	*0.341*
Dual loop diuretics	19 (11.2)	23 (20.2)	*0.032*
Ivabradine	18 (10.6)	13 (11.4)	*0.421*
Regular medications	9.0 ± 2.4	9.3 ± 2.6	*0.784*
Hyperpolypharmacy	71 (41.8)	50 (43.9)	*0.435*
Discharge Guideline Adherence Indices			
GAI-3 (%)	45.2	45.7	*0.598*
Adjusted GAI-3 (%)	50	52.6	*0.854*
GAI-Target dose (%)	25	23	*0.349*
GAI-5 (%)	51.6	48.4	*0.632*
High-GAI	81 (47.6)	55 (48.2)	*0.881*
Potentially inappropriate prescribing in Heart Failure			
Any PIMHF item	29 (17.1)	22 (19.3)	*0.651*
Non-dihydropyridine CCB	18 (10.6)	7 (6.1)	*0.627*
Pregabalin	1 (0.6)	9 (7.9)	*0.015*
Oral corticosteroid	4 (2.4)	6 (5.3)	*0.845*
Medicinal formulations with high sodium content	8 (4.7)	2 (1.8)	*0.746*
Thiazolidinediones (-glitazones)	1 (0.6)	0 (0.0)	*0.642*

Comparisons were made between Heart Failure care provided before and after the implementation of clinical pharmacy service at the critical care unit. Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean ± standard deviation. **Abbreviations:** CCB, calcium channel blocker; EBBB, evidence-based beta-blocker; GAI, guideline adherence index; MRA, mineralocorticoid receptor antagonist; PIMHF, potentially inappropriate medicines in heart failure; RASi, renin-angiotensin system inhibitor (ACE inhibitor/angiotensin-II receptor blocker).

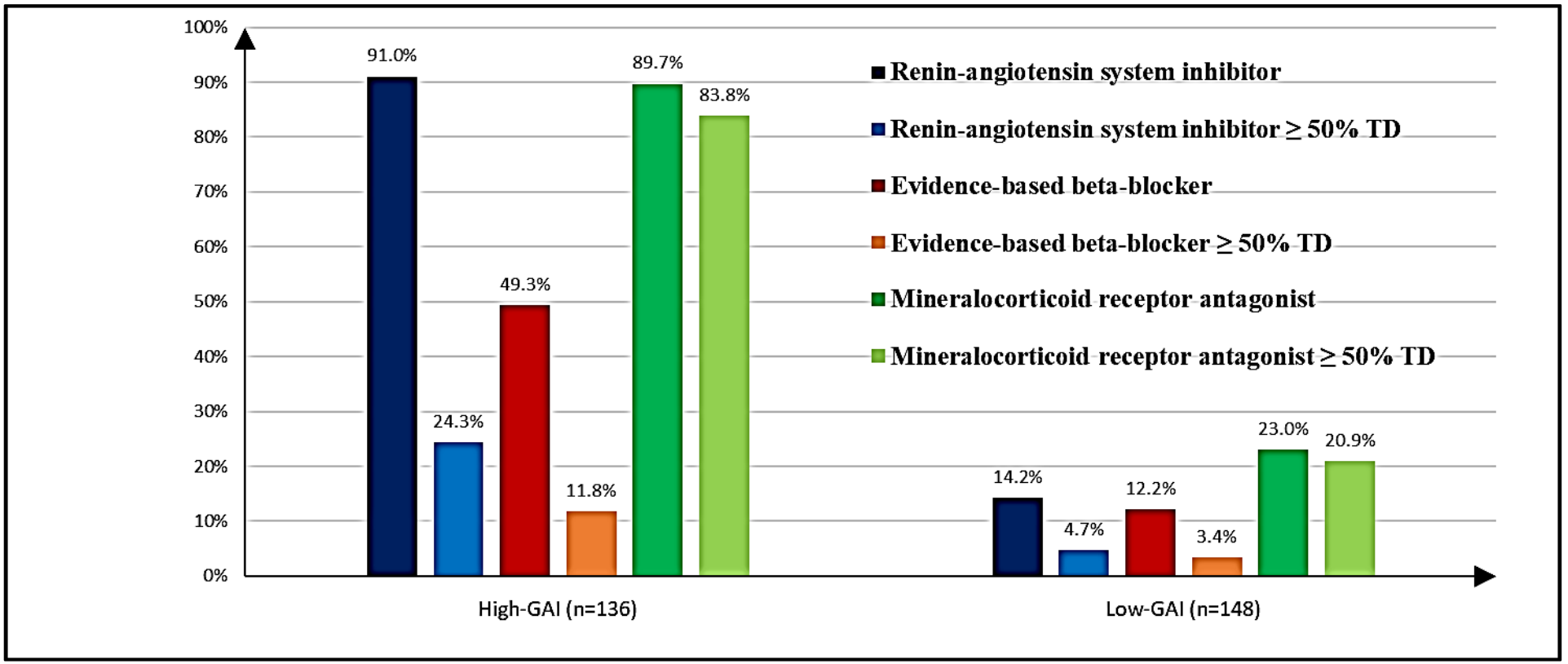


Figure 6.1 Prescription of guideline-directed medical therapies and achievement of 50% target dose for each medication class, presented as Low-GAI population and High-GAI population.

The proportion of patients prescribed each medication class was compared between High-GAI and Low-GAI populations. This comparison for each of the three GAI medicines was statistically significant *(p-value < 0.001)*.
The proportion of patients prescribed ≥ 50% target dose of each medication class was compared between High-GAI and Low-GAI populations. This comparison for each of the three GAI medicines was statistically significant *(p-value < 0.001)*.

The target dose is defined in Table 6.1. **Abbreviations**: GAI, guideline adherence index; TD: target dose.

6.5 Discussion

The present study represents the first application of the GAI and PIMHF prescribing review tools in a critical care setting. Heart Failure prescribing was sizeably deviated from the guideline-directed disease-modifying strategy. At discharge, the mean guideline adherence was 45.5%, and when adjusted for target dose achievement, this reduced to 24.3%. This study showed that the inclusion of clinical pharmacy service in this setting slightly improved the adoption of guideline-led prescribing.

A recent systematic review found that the GAI-3 of studies published in the period from 2005 to 2016, ranged from 14% to 95%, with a mean GAI-3 of 63%. [147] The GAI-3 was first introduced in 2005 [46] and later modified to include contraindications to therapies [176] and target dose. [179] The GAI-3 of this population was lower than the international mean; however, the GAI-3 reported here is comparable to recently reported GAI-3 in Brazil (41%) and China (43%). [147] The study population may also be the sickest of those reported in the literature on the GAI-3, as these patients were at discharge from a critical care setting where prescribers may not place a strong focus on the long-term HF outcomes. [147]

The prescription rates and the High-GAI achievement reported in this study are significantly lower than those reported in QUALIFY, an international registry that included recently discharged Egyptian HF patients. [48] The differences reported here between patients with High-GAI and those with Low-GAI reflect the adverse impact of age and multimorbidity on guideline adherence. Patients with Low-GAI had higher EF; however, they were older, had a higher comorbidity burden and worse kidney function than High-GAI patients. The adjusted GAI-3 takes into account the contraindications to therapy listed in the ESC guidelines. However, in the present study, adjusting for these contraindications had a small effect on

correcting guideline adherence levels. It is possible that prescribers take other considerations into account when prescribing guideline-directed medical therapies. For instance, almost 30% of the population experienced chronic kidney disease, and these patients were significantly less likely to be prescribed High-GAI than patients with normal kidney function. Therefore, this diagnosis is a potential explanation for the omission of RASi and MRA at discharge. [76, 196] A conservative prescribing pattern is seen here, which may represent physicians preferring the short-term cardio-renal stability over the life-saving disease-modifying strategies. [185, 240] It may also represent prescribers' concerns about the risk of adverse drug reaction, medication costs to the patient and the burden of hyperpolypharmacy. [185, 240]

In the present study, there is a high prescription rate of loop diuretics and MRAs which may indicate physician's preference for the low-priced fixed-dose combinations such as 'furosemide/spironolactone' containing products that are available on the Egyptian market. These affordable products may enhance patient's compliance and persistence. Furthermore, a high incidence of diuretic resistance has been reported among Egyptian patients, and adjunct medications such as metolazone are not commonly included in the hospital formularies. [16, 241] The prescription of this fixed-dose formulation contributed to higher target dose achievement among patients prescribed MRA than the other guideline-directed medical therapies at discharge. The inaccessibility of adjunct diuretics such as metolazone may also have contributed to the unexpectedly high rate of prescription of two or more loop diuretics.

In the present study, there was a low rate of target dose achievement. However, this low rate possibly reflects the critical care setting from which the recently stabilised patients are being discharged, the focus of prescribers on acute illness rather than long-term outcomes and an assumption that doses may be titrated upwards in an ambulatory setting. For instance, 53% of patients in the 'BIOSTAT-CHF' study required a 12-week stepwise approach to reach ≥ 50%

of the recommended target dose. [76] This implies a requirement of the ambulatory care services to provide long-term care plans to uptitrate HF medications as recommended. However, it is of note that in Egypt, outpatient follow-up and monitoring in chronic diseases are not optimal. [121, 125]

The prescription rate of PIMHF items in the present hospital discharge population (18.1%) is slightly higher than that reported in an ambulatory European one (14.6%). [112] The high prevalence of hyperpolypharmacy and multimorbidity among this critically-ill population may contribute to this higher rate. This may be explained by the fact that the patients included in this study were recently stabilised following a critical emergency admission to the unit, implying disease progression and a higher number of medications compared to more stable HF populations. [112] A small but non-significant difference was observed in the prescription of PIMHF items between High-GAI and Low-GAI cohorts. Interestingly, the rate of PIMHF prescription marginally increased after the introduction of a clinical pharmacy service. This was driven by an increase in the prescription of pregabalin. The indications for pregabalin prescription have expanded in recent years, and its prescription rates have increased accordingly. The use of this medication in HF patients is cautioned as it is associated with increasing peripheral oedema. [238] It is possible that the indication for this medication outweighs any prescriber concerns. This latter point would seem at odds; however, with the keen focus of prescribers on HF symptoms as indicated by high rates of diuretic prescription. Alternatively, it may be the case that prescribers and pharmacists are not familiar with such cautions pointing to a need for ongoing medical education on emerging prescribing matters. [238]

The management of HF is complex and multifaceted. As a consequence, guidelines recommend a multidisciplinary approach to the optimal delivery of HF care. [1, 21] Several Egyptian reports

before 2015 show high rates of digoxin use and underutilisation of EBBB, somewhat at odds with the ongoing changes in clinical practice at that time. [15, 16] In the present study, the implementation of a clinical pharmacy service significantly increased the EBBB prescription by 14.5% and significantly decreased digoxin prescription by 10%. The prescribing changes reported here indicate optimised adherence of routine practice to the most recent ESC guidelines. [1] However, the overall GAI-3 and the proportion of patients achieving High-GAI did not significantly increase with the introduction of clinical pharmacy. The pharmacists in this study could make a recommendation about patient medications but had no authority to make changes to inpatient or discharge prescriptions. Reports from Egypt and other MENA countries indicated that physicians are reluctant to alter a colleague's prescription despite appropriate recommendations made by pharmacists. [242-244] This may have the effect of reducing the impact of the pharmacist service. Elsewhere, studies suggest that the acceptance rates for clinical pharmacist interventions in HF and acute coronary syndrome patients range from 70-81%. [204, 239] Unfortunately, the prescribing interventions recommended by pharmacists in this study were not recorded on the unit electronic medical records; therefore, we cannot assess the uptake percentage of these interventions. Moreover, without knowing what the clinical pharmacists' recommended interventions, it is not possible to ascertain if the focus of their interventions was on guideline-led prescribing and disease-modifying therapies. It is possible that pharmacists focussed their efforts on inpatient issues such as therapeutic drug monitoring, renal dose adjustment and intravenous to oral switching or that in some patients, morbidities other than HF were the focus of the pharmacist and prescriber.

6.6 Limitations

Some limitations must be acknowledged in this study. The present study is retrospective, single-centred and includes only the discharge medications of critically-ill patients with HF.

However, the setting is the largest CCU in Egypt. This work was conducted in 2013 – 2017, before the widespread adoption of sacubitril-valsartan in HF care. However, cost implications may limit the use of this drug in Egypt in the short term. Therefore, the authors believe that the focus on prescription and dose of RASi in the present study is warranted. Unfortunately, the rationale for initiating, maintaining, or discontinuing therapy during hospitalisation or at discharge was not recorded on the electronic medical records, and such information may have explained further the findings of this study.

6.7 Conclusion

Our study is the first to comprehensively consider HF guideline adherence, potentially inappropriate prescribing and the role of the clinical pharmacist in a low-middle budget healthcare setting. It highlights some inconsistencies between the recommended HF care and the current routine practice. Although clinical pharmacy services in Egypt are in their infancy, one would expect their impact to increase with time as they have in other jurisdictions.

6.8 Acknowledgements

The research team would like to acknowledge the staff of the Critical Care Medicine Department, Cairo University Hospitals, for their assistance, especially the physicians, clinical pharmacists and information technology team.

7 Chapter 7

Factors Influencing Guideline-Led Prescribing to Heart Failure Patients: A Novel Questionnaire in an Egyptian Critical Care Setting

In the previous chapter, the results showed the moderate adoption of HF guideline-led prescribing at discharge. There are many causative factors that may lead to this. Therefore, the current chapter aims to explore the perspective of the Egyptian prescribers of the same clinical setting in order to describe the full picture of guideline-led prescribing from a second angle: the perspective of prescribers. Evidence from this chapter helps to identify the barriers to guideline-led prescribing in a middle-income Middle-Eastern setting.

7.1 Abstract

7.1.1 Introduction

Heart Failure represents a crucial issue for the healthcare systems in the MENA region due to its considerable human and economic burden. Guideline-led prescribing improves HF patient outcomes, however little is known about the factors influencing guideline-led prescribing to HF patients in Egypt.

7.1.2 Aims

To assess the behaviours and perspective of prescribers in the Critical Care Medicine Department of Cairo University Hospitals, Egypt, towards HF guideline-led prescribing.

7.1.3 Methods

A descriptive survey was disseminated to all medical staff (n = 62) in the department. The 11-item survey considered the factors influencing physicians' HF prescribing practice.

7.1.4 Results

The response rate was 54.8% (n= 34). The international HF guidelines were the primary source of prescribing information for 84.2% of respondents. Staff were more familiar with the latest ESC guidelines' recommendations than Associate Staff (86.7% vs 36.8%, *p-value = 0.012*) and considered patient's perspectives more often (86.7% vs 26.3%, *p-value = 0.036)*. Renal functions were the clinical factor most frequently influencing the prescribing of loop diuretics or RAASi. Pulmonary functions influenced beta-blockers prescription. Patient gender did not

affect the prescription of loop diuretics or RAASi but did influence the prescription of beta-blockers. The most frequently cited barrier to guideline-led prescribing was the absence of locally-drafted guidelines. A majority of prescribers agreed that implementation of clinical pharmacy services, physician education and electronic reminders might improve the implementation of guideline-led prescribing.

7.1.5 Conclusion

Although experienced physicians are familiar with and use international guidelines, all physicians would welcome local guidance on HF prescribing and more significant clinical pharmacist input.

7.2 Introduction

Heart Failure clinical practice guidelines are a robust evidence-based tool for prescribers to manage medication decisions for patients with this complex disease. [1] Application of the guidelines improves the quality of prescribers' clinical decisions and promotes consistent and standardised care. [1, 48] Heart Failure guideline-led prescribing leads to beneficial clinical outcomes in terms of patient's mortality, morbidity and quality of life. [48, 76] Therefore, optimisation of HF guideline-directed medical therapies is strongly recommended during and after acute decompensation of the disease. [1] However, international reports suggest that prescribers do not optimally adhere to the recommended HF guideline-led prescribing at discharge from certain clinical settings. [48, 147] In one study, more than one-third of eligible HF patients have not been prescribed the full list of the recommended HF guideline-directed medical therapies at discharge [48] and elsewhere, only 50% of patients achieved the recommended target doses of the HF guideline-directed medical therapies. [76]

Many physicians report poor awareness of the latest guidelines' recommendations. [245, 246] A national survey in the UK showed that 73% of cardiologists use the HF guidelines in managing the disease. [202] The SHAPE survey indicated that guidelines have only a modest influence on physicians' prescribing decisions; for instance, just 34% of the European cardiologists reported the use of HF guidelines in their daily prescriptions. [155]

Guideline-led prescribing in HF may be challenging due to patients' age [183], gender [143], low BP [146], renal dysfunction [146], presence of pulmonary disorders [184] and the complexity of medication regimens [185]. Women and the elderly are generally under-represented in clinical trials, which may lead to physician uncertainty as to the applicability and safety of guideline-

led prescribing to these patients. [203, 247] The high risk of medication-related adverse events and contraindications to medications also represent major barriers to guideline-led prescribing. [155, 203] Furthermore, the lack of resources and the geographical location impede the affordability and applicability of prescribing the full list of HF indicated medications. [246, 248, 249] For instance, the prescription rates of guideline-directed medical therapies range from 30% in Egypt [16] to 50% in Brazil, [171] and up to 85% in Germany [164].

There is a lack of data quantifying prescribers' preferences regarding potential facilitators for improving guideline-led prescribing in HF. [203, 245, 246] Pharmacists are uniquely positioned to address medication-related problems in order to optimise guideline-led prescribing during and after hospitalisation. [204, 239] Implementation of clinical pharmacy services has been shown to reduce HF rehospitalisation rates by up to 20%. [239] Electronic clinical reminders have also demonstrated a positive impact on prescribing quality and the reduction of medication errors in HF patients. [250]

In the MENA countries and particularly Egypt, no survey or qualitative research has been conducted in the field of HF prescribing practice. [155, 251] Also, the effect on HF prescribing practice of language, culture, healthcare system and the acceptance of clinical pharmacy in the medical team has not been studied in the MENA literature. [243, 244]

7.2.1 Aims

This study aimed to assess the behaviours and perspective of critical care physicians towards prescribing to HF patients and to investigate the potential barriers and solutions to HF guideline-led prescribing in a critical care setting.

7.3 Methods

7.3.1 Ethical consideration

The Research and Ethics Committee of Future University in Egypt granted the ethics approval for the study (*Serial number REC – FPSPI – 11/76*), (Appendix 7). The management board of the Critical Care Medicine Department, Cairo University Hospitals granted permission for the work to proceed in the department. Written information about the study was provided prior to participation, and all participants provided informed consent prior to survey completion.

7.3.2 Study design and measurements

In absence of relevant surveys, a new survey was designed to be customised to Egyptian prescribing practice, cultural, hierarchical and social systems that might be different from Western European countries. The survey was developed with a focus on HF guideline-directed medical therapies and was informed by the results of Chapter 6 of this thesis. [155, 243, 251-254] This descriptive survey was designed in line with the Academy of Critical Care: Development, Evaluation and Methodology recommendations. [255] The development of the survey items was informed by (i) the class I recommendations of the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2016 [1] and (ii) the current literature on guideline-led prescribing. [147, 184, 246, 256] After the first draft of the questionnaire was developed, face validity was tested using a convenience sample of three Critical Care Medicine Department medical staff members who were independent of the study team. Further iterations of the questionnaire were then developed until a final agreement was reached by all authors. The study was written in the English language, as this is the language used professionally in

the department and the language used in medical education in Egypt. A native English speaker (MB) reviewed the questionnaire to ensure its clarity.

The final version consisted of an 11-item questionnaire with 10 choice-questions and one open-ended question (Appendix 8). Seven choice-questions used a 5-point Likert scale that allowed the choice of one single answer only. For six questions, the Likert scale was anchored by *'Never'* and '*Always'* and for one question, it was anchored by '*Completely Unfamiliar'* and '*Very Familiar'*. The open-ended question was optional.

7.3.3 Data collection

All 62 physicians working in the Critical Care Medicine Department were invited to complete the questionnaire. There are different grades of the medical staff in the department: (i) Associate Staff who are junior residents and senior residents; and (ii) Staff who are specialists (Master's degree) and consultants (Doctor of Medicine degree). Dissemination of the questionnaire was via hardcopy or electronically. The hardcopy of the questionnaire was distributed to Staff at the monthly departmental clinical meeting and was distributed to Associate Staff during their scheduled morning shifts in July and August 2018. An identical electronic version of the questionnaire was hosted on the Survey Monkey website (www.surveymonkey.com), and a link to this was distributed via the institutional email addresses and the LinkedIn profiles (where available) of the 62 physicians. The electronic questionnaire was open to receiving responses from July - November 2018. One reminder message was sent via the institutional email system. All responses were recorded anonymously. No incentive was offered to respondents to participate in the study.

7.3.4 Statistical analysis

The study population was subdivided based on the physician's position as Staff or Associate Staff. Data were analysed using SPSS® version 22.0 for Microsoft Windows 10. Categorical data were compared using the Chi-square test or Fischer's Exact test. All statistical tests were exact two-tailed tests, and a $p\text{-}value < 0.05$ was regarded as statistically significant. The percentage of respondents who only chose *'Often'* or *'Always'* answers to the Likert scale questions were reported to enable a clear differentiation between the most and least important factors.

7.4 Results

7.4.1 Completion and response rates

The survey was returned by 34 of the 62 physicians giving a response rate of 54.8%. All the medical grades were represented among the respondents with 15 Staff (44.2%) and 19 Associate Staff (55.8%) completing the survey. The breakdown of the respondents was as follows: junior residents, n = 8; senior residents, n = 11; specialists, n = 4; and consultants, n = 11. Thirteen responses were collected via the electronic questionnaire; the remainder of responses were collected via the hardcopy. All respondents completed the questionnaire in full.

7.4.2 Information sources for prescribing Heart Failure medicines

Responses to the sources of information that guide the respondents are provided in Figure 7.1. International clinical practice guidelines were the most frequently used sources of information with 84.2% of respondents reported using these; however, Staff were more likely to use the international clinical guidelines than Associate Staff (100.0% vs 68.0%, *p-value = 0.027*). Half of the respondents stated that they rely on their own clinical knowledge. A minority (2.9%) of the respondents reported that they used informal information sources such as *Facebook* medical groups; however, no respondent reported accessing information in the Egyptian National Formulary or the informal local medical books. Two or more sources of prescribing information were chosen by 64.7% of respondents.

7.4.3 Familiarity with and adherence to guidelines

Respondents were asked to rate their familiarity with the most recent European HF guidelines (Figure 7.2). A majority of respondents (55.9%) described themselves as *'Familiar'* or *'Very Familiar'* with these guidelines. Staff were more likely to be familiar with these guidelines than Associate Staff (86.7% vs 36.8%, *p-value = 0.012)*. Notably, 12.5% of Associate Staff reported that they are *'Completely Unfamiliar'* with the latest ESC guidelines. While 76.5% of respondents stated that they '*Always*' or '*Often*' comply with the guidelines' recommendations when prescribing to their HF patients, 10.5% of Associate Staff reported that they *'Rarely' or 'Never'* comply with the guidelines whereas no Staff reported this.

7.4.4 Patient's clinical factors influencing the prescribing choices of Heart Failure medicines

A majority of respondents selected renal functions (88.2%) and serum potassium (85.3%) as the patient factors that influence them when prescribing a loop diuretic (Table 7.1). Associate Staff were more likely to be influenced by the patient's pulmonary functions when prescribing a loop diuretic than Staff (73.7% vs 33.3%, *p-value = 0.036*). When prescribing a RAASi, the majority of respondents reported that they are influenced by serum potassium level (88.2%), renal functions (85.3%) and BP (79.4%). When prescribing a beta-blocker, HR (88.2%), BP (82.4%) and pulmonary functions (76.5%) were the patient factors most likely to influence prescribers. Just 5.9% stated that HR is not a factor that influences their prescribing of beta-blockers. In prescribing loop diuretics and RAASi, few prescribers reported being influenced by patient gender. However, gender was reported as a consideration when prescribing a beta-blocker by 29.4% of respondents.

7.4.5 Discussion of medication choice with patients

Respondents were asked if they discuss medication choice with their patients, and 44.1% of respondents stated that they '*Always'* or '*Often'* do so. Staff were more likely to discuss medication choice with patients than Associate Staff (86.7% vs 26.3%, *p-value = 0.036*). Conversely, 17.6% of respondents reported that they never discuss medication choice with their patients.

7.4.6 Barriers to prescribing the guideline-directed medical therapies

Respondents were asked to what extent they considered specific issues to be a barrier to prescribing the guideline-directed medical therapies to their HF patients (Figure 7.3). The most frequently chosen options were the lack of hospital guidelines (79.4% *Always/Often*); medication cost (76.5% *Always/Often*); and lack of national guidelines (67.6% *Always/Often*). The most frequently cited barriers for Staff were the lack of national guidelines and the lack of hospital guidelines (80.0% *Always/Often* for both) while Associate Staff most frequently cited medication cost as a barrier to guideline-led prescribing (84.2% *Always/Often*). The workload was deemed a barrier by Associate Staff more than by Staff (52.3% vs 13.3%, *p-value = 0.026*).

7.4.7 Potential actions to improve Heart Failure prescribing outcomes

Respondents were asked what potential solutions they believed could be implemented in order to optimise guideline-led prescribing (Figure 7.4). The greater involvement of clinical pharmacists in HF patient care was identified as a potential solution by 67.6% of respondents while regular email bulletins about HF medicines was chosen by 64.7% of respondents. Differences emerged between Staff and Associate Staff preferences. Staff were supportive of

clinical pharmacist involvement in patient care (73.3% chose this option) but were least supportive of receiving education from clinical pharmacists (53.3% chose this option). Associate Staff were most supportive of receiving regular emails about HF medicines (68.4% chose this option) and least supportive of using the hospital information technology (IT) system to receive prescribing recommendations for individual patients (42.1% chose this option). More than one solution option was chosen by 35.3% of respondents.

Table 7.1 Patient clinical factors influencing the prescribing choices of heart failure guideline-directed medicines, N = 34 respondents.

% of respondents who only chose '*Often*' or 'Always'	Total (n = 34) N (%)	Associate Staff (n = 19) N (%)	Staff (n = 15) N (%)
Loop diuretic			
Age	10 (29.4)	5 (26.3)	5 (33.3)
Blood pressure	22 (64.7)	10 (52.6)	12 (80.0)
Gender	2 (5.9)	2 (10.5)	0 (0.0)
Heart rate	12 (35.3)	8 (42.1)	4 (26.7)
Liver functions	7 (20.6)	5 (26.3)	2 (13.3)
Pulmonary functions*	19 (55.9)	14 (73.7)	5 (33.3)
Renal functions	30 (88.2)	16 (84.2)	14 (93.3)
Serum potassium	29 (85.3)	15 (78.9)	14 (93.3)
Renin-angiotensin aldosterone system inhibitor			
Age	12 (35.3)	7 (36.8)	5 (33.3)
Blood pressure	27 (79.4)	13 (68.4)	14 (93.3)
Gender	3 (8.8)	3 (15.8)	0 (0.0)
Heart rate	9 (26.5)	7 (36.8)	2 (13.3)
Liver functions	7 (20.6)	2 (10.5)	5 (33.3)
Pulmonary functions	11 (32.4)	8 (42.1)	3 (20.0)
Renal functions	29 (85.3)	15 (78.9)	14 (93.3)
Serum potassium	30 (88.2)	16 (84.2)	14 (93.3)
Beta-blocker			
Age	13 (38.2)	9 (47.4)	4 (26.7)
Blood pressure	28 (82.4)	17 (89.5)	11 (73.3)
Gender	10 (29.4)	5 (26.3)	5 (33.3)
Heart rate	30 (88.2)	18 (94.7)	12 (80.0)
Liver functions	5 (14.7)	4 (21.1)	1 (6.7)
Pulmonary functions	26 (76.5)	15 (78.9)	11 (73.3)
Renal functions	5 (14.7)	4 (21.1)	1 (6.7)
Serum potassium	10 (29.4)	7 (36.8)	3 (20.0)

Survey question: When prescribing (i) a loop diuretic, (ii) renin-angiotensin-aldosterone system inhibitor, or (iii) beta-blocker to a heart failure patient, to what extent do the following patient factors influence your prescribing choices? Please use the scale from '*Never'* up to '*Always'*.

Data are presented for the total population, Associate Staff and Staff and the * indicates *p-value* < *0.05* for the comparison between Associate Staff and Staff. The proportion of respondents who indicated *'Often' or 'Always'* in response to the question is given.

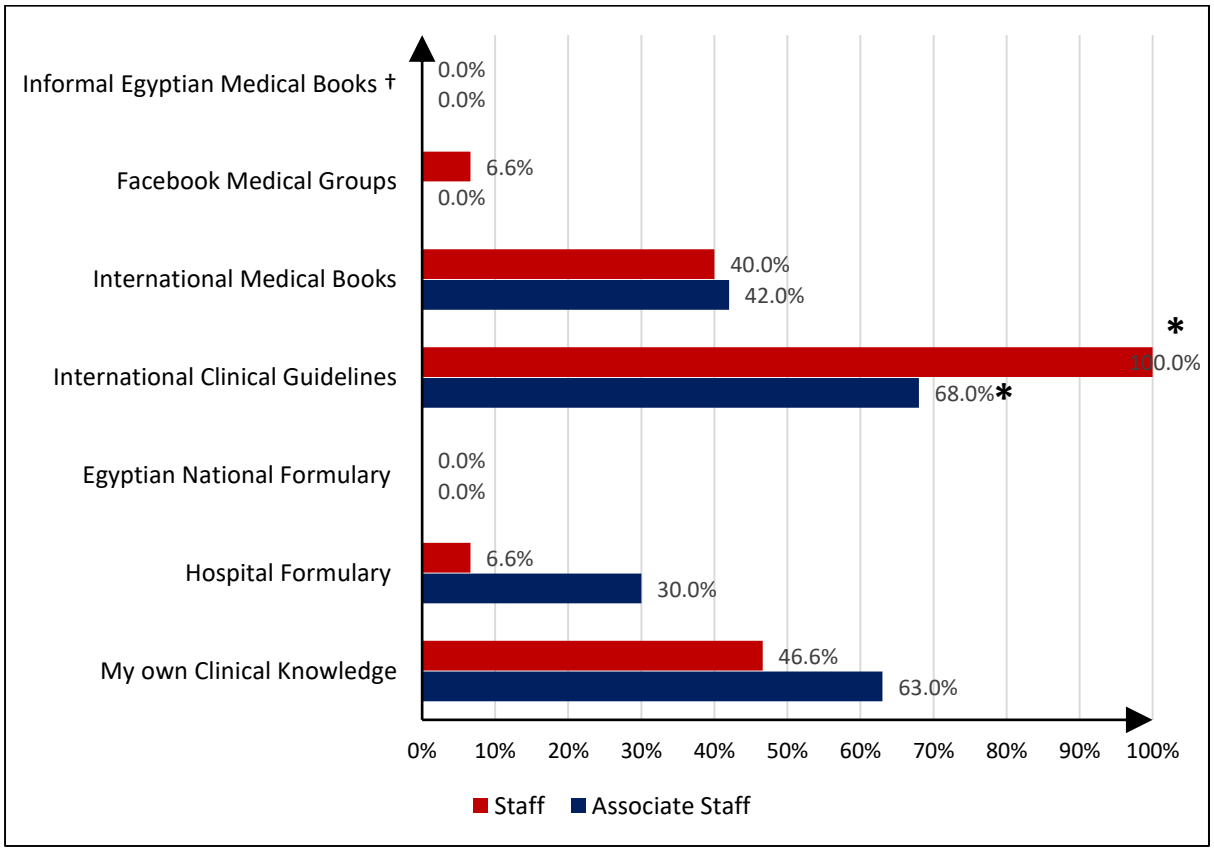


Figure 7.1 Information sources for prescribing Heart Failure guideline-directed medical therapies.

Survey question: What information sources guide you for prescribing Heart Failure medicines? You may choose more than one option.

Data are presented as Staff (specialists and consultants), and Associate Staff (junior and senior residents) and the * indicates *p-value* < *0.05* for the comparison between the two groups.

† Informal Egyptian medical books refer to empiric books that are written by undergraduate medical students or medical residents, citing their clinical experience without referencing the written information.

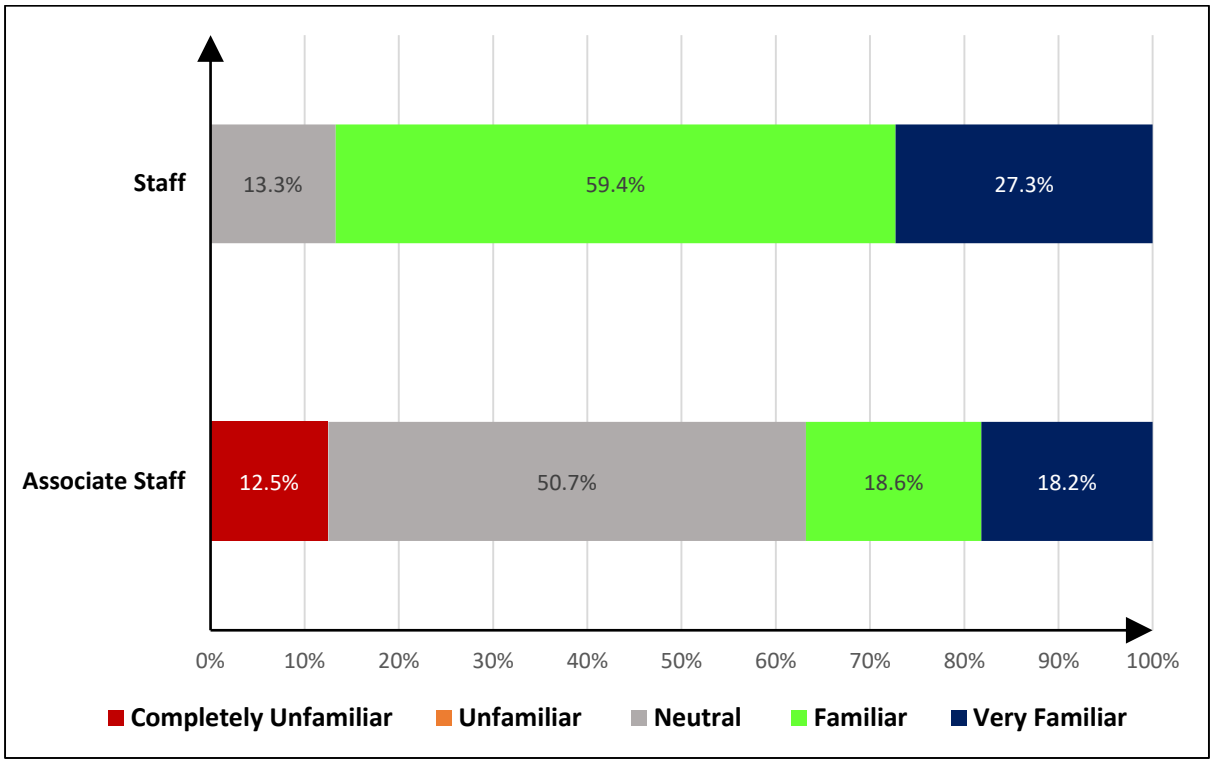


Figure 7.2 Familiarity of respondents with the European Society of Cardiology Guidelines on the Management of Acute and Chronic Heart Failure. [1]

Survey question: The European Society of Cardiology published a new guideline on Acute and Chronic Heart Failure in 2016. Please rate your familiarity with this guideline using the scale from '*Completely Unfamiliar*' up to '*Very Familiar'*.

Data are presented as Staff members (specialists and consultants) versus Associate Staff (junior and senior residents).

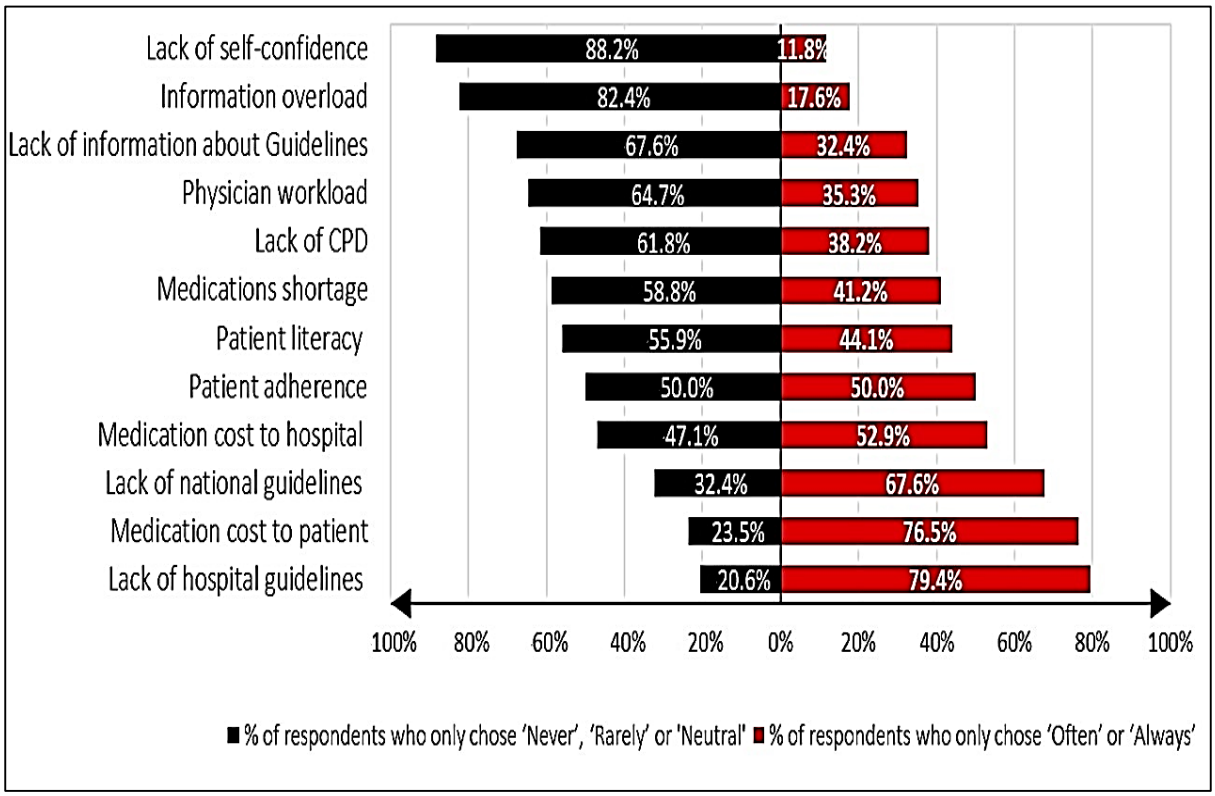


Figure 7.3 Barriers to prescribing the guideline-directed medical therapies from the perspective of respondents.

Survey question: To what extent do you agree or disagree that each of the following is a barrier / obstacle to prescribing guideline-directed therapies in your patients? Please use the scale from '*Never*' up to '*Always*'.

Data are presented for the total population. The proportion of respondents who indicated 'Often' or '*Always*' in response to the question is drawn in red bars (right bars) while the proportion of respondents who indicated '*Never*', '*Rarely*' or '*Neutral*' is drawn in black bars (left bars). **Abbreviations:** CPD, continuous professional development.

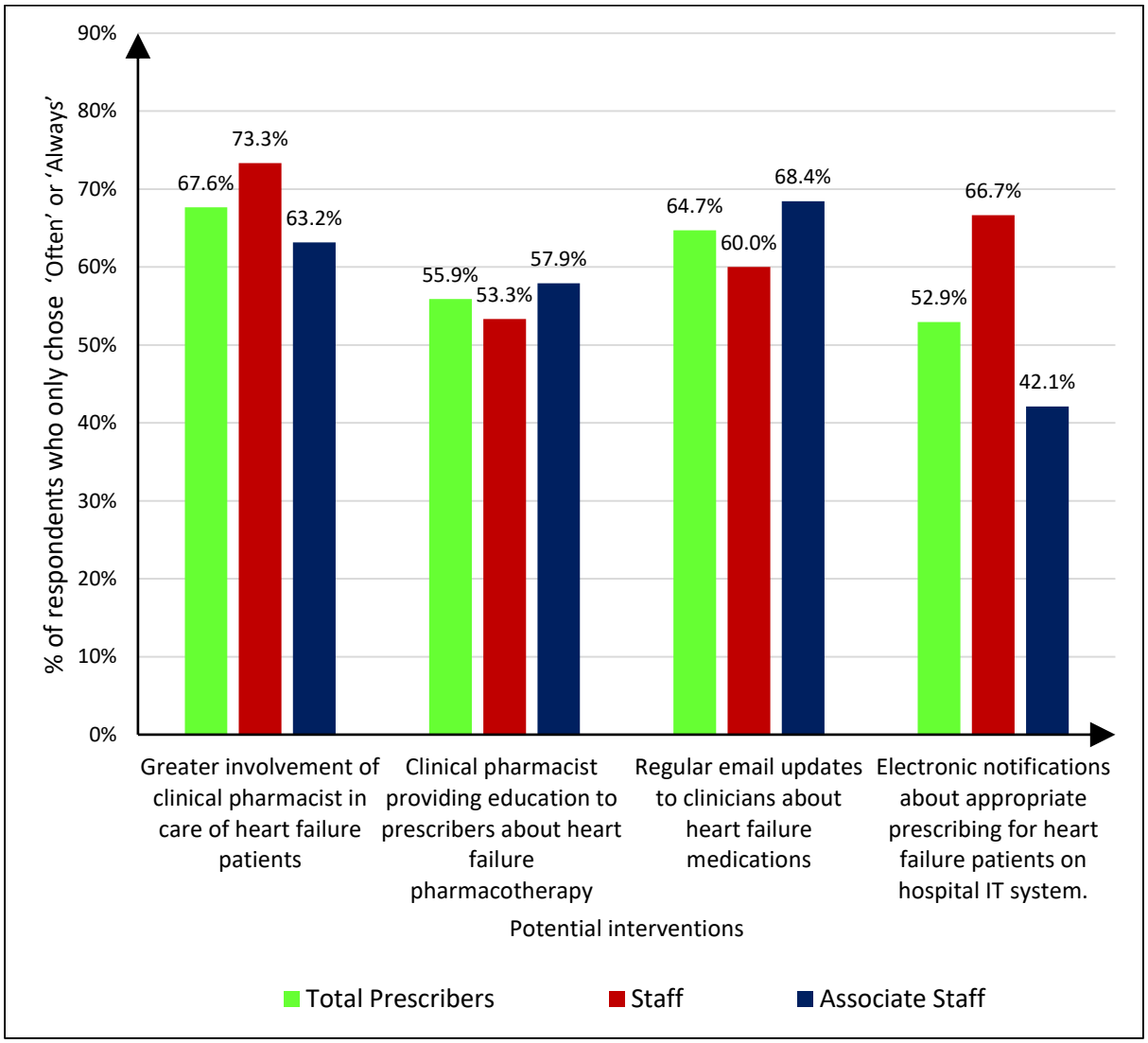


Figure 7.4 Potential actions to improve Heart Failure prescribing outcomes from the perspective of respondents.

Survey question: To what extent do you agree that each of the following actions would help you to improve Heart Failure prescribing outcomes? You may choose more than one option.

Data presented for the total population, Associate Staff and Staff. The proportion of respondents who indicated '*Often*' or '*Always*' in response to the question is given. **Abbreviations**: IT, information technology.

7.5 Discussion

This survey is a novel analysis in the HF literature quantifying the perspectives and behaviours of prescribers in a critical care setting regarding the evidence-practice mismatch for prescribing in HF. The majority of respondents use the international guidelines, and over half are familiar with the most recent guidelines. However, over three-quarters of respondents identified the lack of locally-drafted guidelines and the cost of medications to the patient as limiting their adherence to guideline-led prescribing practice. Furthermore, the respondents identified vital solutions to improve guideline-led prescribing, including enhancement of clinical pharmacist role and electronic interventions.

Clinical practice guidelines serve as a framework for clinicians managing HF patients. [1] The current international guidelines were identified as the most frequently used sources of HF prescribing information in the present setting, particularly amongst Staff. This suggests that greater postgraduate clinical experience changes prescribers practice and that more junior clinicians may continue to rely on knowledge gained in medical school where guideline-directed care may not be strongly emphasised. [257] This evidence-based knowledge of the Staff members was positively translated into two prescribing practices demonstrated in their responses. First, the Staff members placed higher importance on discussing medications with their patients, which is strictly in line with the latest ESC guidelines' recommendations. [1] Secondly, Staff broadly supported the greater implementation of clinical pharmacy services and electronic updates. This support reflects an understanding of the important role of the multidisciplinary teamwork to offer a guideline-directed HF care. [1, 239, 258]

Low prescribing rates of beta-blockers have been reported among Egyptian HF patients. [16, 143] The Long-Term Registry of Egypt demonstrated a considerable underutilisation of beta-blockers regardless of gender or HF severity. [16, 143] In the present survey, 77% of respondents identified pulmonary functions as a factor to consider prior to prescribing a beta-blocker. In the SHAPE survey, poor pulmonary functions were identified by 68% of respondents as a reason for beta-blocker omission or discontinuation. [155] In a UK-based study, poor pulmonary functions were reported as the major reason for omitting beta-blocker prescription in up to 11% of eligible ambulatory HF patients. [184] According to the ESC guidelines [1], chronic obstructive lung disease or dyspnoea are not contraindications to beta-blocker therapy; however, it appears that there is ongoing clinician concern regarding the risk of beta-blocker-induced bronchospasm despite evidence of patient tolerance and confirmed safety of beta-blockers in pulmonary diseases. [259, 260]

Clinicians reported that gender influenced the prescribing of beta-blockers but not the prescribing of RAASi or loop diuretics. The Egyptian HF Long-Term Registry found that compared to males, female HF patients were less likely to receive guideline-recommended loop diuretics and RAASi due to their different comorbidity and cardiovascular risk factors profiles.[143] However, the same registry found a considerable underutilisation of beta-blockers regardless of gender. The discrepancy between the registry findings and the current survey results might reflect concerns related to the adverse drug reaction profile of beta-blockers. [184] The onset of HF occurs a decade younger in the Egypt population than in European or North American populations, and adverse events may exert a greater effect on the quality of life of these younger patients.

The survey inquired about the barriers to implementation of HF guidelines at the level of the patient, physician and healthcare setting. The lack of locally- or nationally developed guidelines was cited as a substantial barrier to guideline-led HF care by over 75% of respondents. The barriers identified in the current survey are similar to previous reports from Europe and the USA, [202, 203, 256] where this has been reported as a barrier in primary care settings. [202, 256] Several reasons may explain this barrier in a hospital-based setting. First, the HF clinical trials are often highly selective and may not include patients whom physicians consider to be similar to the real-world patients. [202, 247] This disparity may lead to physician uncertainty about guidelines' applicability, particularly in an HF population who might be older, multimorbid or acutely-ill. [155, 202]

The evidence-practice mismatch is of particular importance in low-middle income countries. [122, 246, 248, 249] International evidence illustrates the adverse effects of limited patient literacy and socio-economic status on HF clinical outcomes and management in terms of prescription of medications, use of device-based therapy, patient adherence and even mortality. [248, 249] This may be why 50% of the survey respondents stated that they base their clinical decisions on their clinical experience rather than on guidelines. The setting of the survey in a middle-income country may also explain why respondents consider medication cost as an important barrier to guideline-led prescribing. In this setting, costs to the patient or the healthcare provider may constrain the prescriber in the provision of some of the recommended long-term therapeutic strategies. [122, 246, 248, 249] In a European HF population, the prescription rates of the guideline-recommended therapies exceeded 85% of patients [164] while the cost implications of some medications and the lack of standardised outpatient records may limit the prescription of the full list of medications in some Egyptian settings. [16, 122]

Respondents supported the greater implementation of clinical pharmacy services as a means to improve guideline-led prescribing. This solution was supported more strongly by Staff than by Associate Staff. The inclusion of clinical pharmacy services in the HF multidisciplinary team is endorsed by several guideline authorities. [1, 258, 261] Clinical pharmacists in hospitals are uniquely positioned to manage prescribing problems encountered by prescribers in caring for complex and often multimorbid HF patients. [204, 239] In Canada, the inclusion of a clinical pharmacist in an HF multidisciplinary team brought about a significant reduction in patient mortality over a four-year follow-up period. [258] Elsewhere, the inclusion of clinical pharmacy services in HF care reduced rehospitalisation rates by 20%. [204, 239] The acceptability of clinical pharmacy in the present study would seem at odds with previous reports from Egypt and other MENA countries that showed prescribers' reluctance to alter a colleague's prescription despite the appropriate course of action recommended by the pharmacist. [242, 243] Staff were also in favour of electronic notifications about prescribing in individual HF patients while Associate Staff preferred email updates about HF prescribing. While such interventions may be effective [250], it has been shown that multiple and repetitive electronic interventions can lead to a risk of alert fatigue and the prescriber may be less likely to accept the suggested interventions due to desensitisation or cognitive overload. [262]

7.6 Limitations

The majority of eligible prescribers completed the survey in full, and there is a balance of Associate Staff and Staff responses. However, it is possible that survey non-responders may have expressed different perspectives to those expressed by respondents. To maximise response rates and minimise this risk of bias, we used a systematic method for following-up

with the non-responders and made the study questionnaire available in both paper and online formats. Also, qualitative data would be useful to confirm some of the findings.

7.7 Conclusion

Experienced physicians are familiar with and use international guidelines in their prescribing practice; however, a majority of prescribers in this setting would welcome local HF prescribing guidelines and more significant input from clinical pharmacy services. The work presented here has implications for future studies designing locally-drafted guidance to make the international HF guidelines actionable and applicable in a middle-income setting and taking into account the clinical complexity of many HF patients.

7.8 Acknowledgements

The authors would like to thank Ms Dina Mahmoud, Clinical Pharmacist in the Critical Care Medicine Department for her assistance in data collection.

8 Chapter 8

Overall Discussion and Conclusions

This chapter summarises the key findings from this programme of research and discusses the contribution of the thesis to the current literature. The clinical implications of the research are highlighted, and the strengths and limitations of the work are discussed, alongside providing recommendations for future research.

8.1 Introduction

The overarching aims of this PhD thesis were:

firstly, to assess the level of adherence to the guideline-led prescribing and to identify the potential barriers to its adoption in the routine clinical practice in Ireland as a European country of high income and Egypt as a MENA country of medium-income; and secondly, to determine the prevalence of potentially inappropriate prescribing in HF context in the same clinical settings.

The series of research presented in this thesis is the first to combine the assessment of HF prescribing from the two angles of medical prescribing practice: appropriate and potentially inappropriate in order to comprehensively explore the potential opportunities for improvement and the relationship between the two types of medical prescribing practice in HF. The initial five chapters addressed the general aims and objectives of this thesis, while this final chapter aims to review and interpret the results from this programme of research and to discuss their contribution to the current literature. The key prescribing patterns in the three clinical settings discussed in Chapters 4 to 6 are presented below (Table 8.1). The clinical implications of the research are highlighted. The strengths and limitations of this work are discussed, and proposals for future work are presented.

Table 8.1 Summary of Heart Failure profile and prescription rates of guideline-directed medical therapies in the Irish and Egyptian clinical settings reported in the thesis.

Study Chapter	Chapter 4	Chapter 5	Chapter 6
Clinical Setting Profile			
Study centre	MUH	14 LTCs	CCU
Prescriber's speciality	Cardiologists	Geriatricians/GPs	Critical Care Physicians
Geographical location	Cork City	Cork County	Cairo
N population	127	265	284
Type of patients	Ambulatory	Ambulatory	hospitalised critically-ill
Type of clinical setting	2ry Care	1ry care	3ry Care
University teaching setting	Yes	No	Yes
Reference ESC Guidelines	2012/2016	2005	2012
Clinical Profile of Patients			
Mean ± SD age (years)	71.7 ± 13.1	84.8 ± 7.4	66.7 ± 11.5
Patients ≥ 80 years	30.70%	71.30%	12.30%
Mean number of comorbidities	7.4 ± 2.7	11.6 ± 3.5	5.2 ± 2.4
Hypertension	62.2%	49.4%	49.3%
Coronary artery disease	30.7%	32.5%	46.5%
Target HR ≤ 70 bpm	31.5%	42.3%	37.7%
Medications Profile of Patients			
RASi	67.7%	24.2%	51.4%
RASi ≥ 50% Target Dose	52.7%	10.6%	14.8%
EBBB	77.2%	22.6%	29.9%
EBBB ≥ 50% Target Dose	47.2%	6.0%	7.4%
MRA	26.0%	4.9%	54.9%
MRA ≥ 50% Target Dose	18.9%	4.5%	51.5%
Dual loop diuretics	4.7%	0.0%	15.2%
No HF-related therapy prescribed	6.3%	8.3%	4.9%
High-GAI achievement	63.0%	54.7%*	47.9%
Mean number of regular medications	8.2 ± 3.1	9.2 ± 3.2	9.1 ± 2.5
Hyperpolypharmacy	30.7%	32.8%	43.7%
Multivariable analysis **Positive** clinical factors associated with High-GAI	1) HFrEF	1) Coronary artery disease 2) Comorbidity burden 3) Hyperpolypharmacy	1) HFrEF 2) Absence of CKD 3) Younger age
PIMHF prescription prevalence	19.7%	24.2%	18.1%
NDP-CCB in HFrEF patients	5.5%	-	0.0%
NDP-CCB + EBBB	9.4%	0.0%	0.0%

*High-GAI considered the prescription of renin-angiotensin system inhibitor, beta-blocker, and loop diuretic. **Abbreviations:** CCU, Critical Care Unit of Cairo University Hospitals, Cairo, Egypt; CKD, chronic kidney disease; EBBB, evidence-based beta-blocker; ESC, European society of cardiology; GAI, guideline adherence index; GP, general practitioners; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LTCs, long-term care facilities; MRA, mineralocorticoid receptor antagonist; MUH, Mercy University Hospital, Cork, Ireland; NDP-CCB, non-dihydropyridine calcium channel blocker; NSAIDs, non-steroidal anti-inflammatory drugs; PIMHF, potentially inappropriate medicines in heart failure; RASi, renin-angiotensin system inhibitor.

8.2 Overview of the key findings and contribution to existing knowledge

Assessment based on prescription rates alone is not sufficient to evaluate the prescribing quality in routine clinical practice as they do not consider many important factors such as patient's (i) eligibility for; (ii) contraindication to therapy; or (iii) achievement of the guideline-recommended target dose. Hence, the systematic review (Chapter 3) evaluated studies of the available numerical prescribing review tools for assessing the quality of HF prescribing in clinical practice. [147] Sixteen studies met the inclusion criteria, and thirteen studies were eligible for inclusion in a meta-analysis. The review identified four different measurement tools. The most frequently cited tool was the Guideline Adherence Index (GAI). The international mean of GAI-3 is 63%. High-GAI based management showed a significant survival benefit. It was associated with a reduced risk of mortality (Hazard Ratio 0.29, 95% CI, 0.06−0.51) and reduced rehospitalisation (Hazard Ratio 0.64, 95% CI, 0.41−1.00). However, increasing patient age and comorbidity burden are the most frequently cited barriers to initiation or resumption of the guideline-directed medical therapies. This is conceivable as the more comorbidities the patient has, the less freedom the physician has to prescribe the full list of the recommended medications. [263]

In an update of this systematic review conducted in April 2019, four additional studies were identified. The results of which were consistent with the previously included studies, and thus did not change the conclusion of the published review. All four additional studies were using the new QUALIFY score and were based on data from the QUALIFY global registry. [47, 48, 93, 182] The newly included studies emphasised the survival benefit of the high implementation of guideline-led prescribing among 36 countries. [47, 48, 93, 182]

Chapter 4 identified the gaps in medication use and dosing that persist in an Irish contemporary outpatient practice in the absence of an HF-specific DMP. The international registries and reports revealed the survival benefits of guideline-directed medical therapies. [47, 76, 86, 87] It is therefore evident that unjustified omission, underuse or under-dosing of the recommended medications is not good medical practice. This implies the importance of the optimisation of medications for the ambulatory HF outpatients. [47, 86, 87] The utilisation rates of guideline-directed medical therapies in the study setting were RASi (67.7%), EBBB (77.2%) and MRA (26.0%). These rates add to the fact that managing MRA therapy is more challenging than managing RASi and EBBB therapies. [113, 196] This can be partly interpreted by the fact that MRA therapy is often associated with worsening renal functions and hyperkalaemia. [113, 196, 197]

Additionally, the absence of clinical barriers between HF patients having a High and Low-GAI based management among the study population draws attention to the so-called *'clinical inertia'* in routine outpatient practice. [198, 199] The results showed that no patient achieved the 100% target dose of all three guideline-directed medicine classes. This finding is strictly in line with the longitudinal follow-up study of CHAMP-HF patients. [198, 200] In CHAMP-HF, no outpatient received a medication titration within 12 months post-discharge despite eligibility and absence of contraindications. [198, 200] Also, only 1% of CHAMP-HF outpatients have been prescribed the target dose of all three guideline-directed medicines. [86]

Despite the ESC guidelines' recommendation, the most frequently used PIMHF in the study was the non-dihydropyridine CCB (n = 15, 11.8%). Of which, twelve patients were prescribed a concurrent EBBB (9.4%). Therefore, this study emphasises the need for clinical pharmacy services to overcome clinical inertia in terms of optimisation and uptitration of the guideline-

directed therapies and management of the potentially inappropriate prescribing in outpatient practice. [207, 235]

According to the literature review in Chapter 2, LTC facilities were not included in the HF-specific published literature in Ireland. The international literature on HF found that the omission of the lifesaving guideline-directed medical therapies is usually common in patients who were ≥ 80 years. [109, 264] Long-Term Care residents with HF are often older and suffer from significant physical limitations, cognitive impairment and a high degree of comorbidity as well as complicated drug regimens and problematic polypharmacy. [219] These patients differ substantially from the typical HF patients enrolled in randomised clinical trials, and that might explain the divergence from treatment guidelines. [109, 219, 224] Thus, the aim of Chapter 5 was then to measure the level of guideline-led prescribing and potentially inappropriate prescribing in the Irish LTC facilities as well as identifying the clinical factors associated with High-GAI based management in this vulnerable HF population.

This multi-centre study showed the high reliance of geriatricians and general practitioners (GPs) on loop diuretics prescription as the primary medication in these older HF patients rather than the guideline-directed medical therapies. For instance, loop diuretics were prescribed to 140 patients (52.8%) as HF single therapy. The study found 8.3% of HF patients that were not prescribed any HF-related medications. The study reported the negative impact of reduced renal functions and contraindications on guideline-led prescribing. As prescribed to 10% of patients, NSAIDs were the most frequently prescribed potentially inappropriate medications. Considering that the Cork region contains approximately 15% of the population of Ireland, the results are likely representative of LTC centres nationwide. As the majority of HF literature in LTC facilities focus on the undetected diagnosis or the clinical outcomes, so this study

represents a prescribing review report for the quality and patterns of HF management in LTC facilities. [215, 219, 223, 224] Also, this study confirms previous research findings that the older HF patients who need LTC after discharge from the hospital face higher risks of poor outcomes and poorer quality of management. [212, 215]

The literature on HF prescribing practice in Egypt is very scarce. Chapter 2 showed that the critical care units were not covered by the published Egyptian research regarding HF care. Therefore, the 5-year analysis in Egypt (Chapter 6) aimed to describe the guideline adherence in HF at discharge and to study the potential role for clinical pharmacists to optimise prescribing outcomes in a middle-income healthcare setting of critically- and acutely-ill hospitalised HF patients. Evidence suggests that pre-discharge initiation of the guideline-directed medical therapies not only increases the likelihood of therapy continuation and persistence but also translates into improved clinical outcomes. [1, 265-267] Pre-discharge can be an ideal time to start or resume medications as patients with HF can have appropriate discharge therapeutic plans in a controlled setting, and therefore, the ability to monitor and possibly uptitrate therapy. [1, 265-267]

The study (Chapter 6) in Egypt reflected the deviation of the discharge therapeutic plans from the lifesaving guideline-directed disease-modifying approach. Over the study period, the overall guideline adherence was moderate in comparison to the international numbers. Prescription of the guideline-recommended target dose was also deemed problematic at the discharge point. Among all discharges, 7.4% of patients only were prescribed ≥ 50% of the target dose of EBBB. However, this might be conceivable based on the type of patients in this clinical setting. It is essential to mind that the ESC guidelines were developed in stable HF patients from high-income or Western countries; thus, the recently stabilised patients of

different living conditions and different socioeconomic levels may lack some evidence for a directed physician's practice and clinical outcomes. [249]

Overall, the findings of this study corroborate prior and recent research showing the moderate adoption of guideline-led prescribing in chronic worsening HF patients in Europe and the USA. [235, 236, 268, 269] In a nationwide study in Denmark, Gislason et *al.* found that patients who have not initiated their guideline-indicated medications within 90 days of discharge have a very low probability of later initiation. [225] That is why the current study (Chapter 6) is important to the Egyptian medical practice because it has been reported that outpatient follow-up and monitoring in chronic diseases are not optimal in Egypt. [121, 125] Keeping in mind the lack of standardised outpatient records in the Egyptian hospitals, it is imperative to ensure the appropriate prescription and uptitration of HF medications at the discharge point to ensure the delivery of optimal care. [197] Furthermore, a post-hoc analysis of the *Registry Focused on Very Early Presentation and Treatment in the Emergency Department of Acute Heart Failure* (REALITY-AHF) data examined 1,682 patients hospitalised with acute HF in Japan. [266] This analysis found that the presence of prescriptions for the three guideline-directed therapies (RASi, EBBB and MRA) at discharge was associated with a significant reduction of 70% in one-year mortality. [266]

Then, a question about the benefits of clinical pharmacy service implementation as multidisciplinary care might be raised in this medium-income clinical setting. The service slightly optimised the quality of HF prescribing practice as they significantly improved the beta-blockers prescription rate and reduced digoxin use in line with the latest recommendations of the clinical practice guidelines and international reports. [1, 41, 47] It is of note that beta-blockers underutilisation and digoxin overutilisation are the most important HF prescribing

anomalies in Egypt from 2002 to 2018. [15, 16, 143] Thus, this study represents an effort to improve and assess the uptake of guideline-led prescribing towards HF patients at discharge by the implementation of clinical pharmacy services. [207, 235, 239]

The results of this study led us to conduct a questionnaire in the same unit (Chapter 7). The questionnaire aimed to identify the potential barriers to guideline-led prescribing by elucidating individual reasoning beyond clinical decision-making. The questionnaire provided a new understanding of the reasons behind the suboptimal adherence to the clinical practice guidelines from the perspective of low-middle income countries and particularly, Egypt. The majority of respondents agreed on the limiting effect of kidney functions prior to prescribing the inhibitors of the RAAS. The questionnaire also identified the needs and difficulties faced by prescribers in their routine practice. The most frequently cited barrier to guideline-led prescribing was the absence of locally-drafted guidelines. This barrier may reflect prescribers' uncertainty of the effect of the international guidelines in the Egyptian population. It is of note that HF patients from the Middle-East region were presented only in the EMPHASIS clinical trial, which implies the striking absence of this segment of patients in the landmark clinical trials. [71] Elsewhere, Blum and colleagues found that HF patients with higher socioeconomic levels are less likely to be rehospitalised within the first 30 days of discharge. [270] This implies a mismatch between the HF population of the evidence-based clinical trials and the real-world of HF patients in Egypt. [249] That is why the prescribers might make their decisions based on their personal clinical experience even when the guidelines might recommend a different course of action. In order to improve prescribing quality, a majority of prescribers agreed on the importance of clinical pharmacy services implementation. This finding represents a disparity between the theoretical acceptance of clinical pharmacy presence (Chapter 7) and the actual quantitative results of clinical pharmacy effect as seen in Chapter 6.

Overall, this survey represents an important extension to the European HF surveys SHAPE 2008 and ADDress 2008 but from an Egyptian point of view. [155, 251] Importantly, our survey added the perspective of prescribers regarding the potential facilitators for optimisation of HF prescribing, which is not addressed in any of the aforementioned surveys. Considering that the CCU of Cairo University Hospitals is the largest one in Egypt, so the results are likely to be representative of the other four critical care settings in Egypt. Also, the survey response rate and results demonstrated its feasibility for use in a larger, multi-centre study of HF care as seen in its high completion and response rates as well as its short completion time.

8.3 Comparison of Heart Failure management in Ireland and Egypt

8.3.1 Cardiologists versus non-Cardiologists

One of the important benefits of guideline-led prescribing is to decrease the variation in HF prescribing practice. [1, 78, 82] The prescribing quality of cardiologists in the MUH is more likely to be better compared to the non-cardiologists in the LTC, Ireland or CCU, Egypt in terms of RASi, EBBB, target dose achievement and High-GAI achievement (Table 8.1). [164, 201] This finding is in line with the finding of the systematic review (Chapter 3). [147]

8.3.2 Guideline-directed medical therapies

Neither the cardiologists nor the non-cardiologists in the two countries prescribed RASi to all HF patients. The presence of HFrEF was estimated to be a positive associate of adherence to guideline-led prescribing in the university teaching hospitals (MUH and CCU). This reflects

the critical impact of EF on prescribing practice regardless of the type of clinical setting due to the strong guidelines' recommendation and the wide availability of clinical trials in HFrEF. [4]

In the two university teaching hospitals, there was an Irish reliance for the use of EBBB as single HF therapy while in Egypt, the reliance was for loop diuretics. This may reflect the different perspective of the two prescribers as well as the different clinical status of the studies' populations. In Ireland, it was clear that the guideline-directed disease-modifying approach and mortality reductions were the predominant perspective towards the ambulatory HF patients. In Egypt, HF management is appeared to be guided by the fluid status to prevent fluid congestion and consequently, reduce the rate of healthcare resources utilisation either in terms of rehospitalisation or outpatient clinics visits. [271] Furthermore, it is important to consider that loop diuretics are the cheapest HF medications within all the medication classes. This cost implication is cited as one of the top barriers to guideline-led prescribing in the survey (Chapter 7). Therefore, this might represent a significant motive for the higher use of loop diuretics.

Both university teaching hospitals in Ireland (MUH) and in Egypt (CCU) prescribed a dual loop diuretic therapy to their HF patients ranging from 5% in Ireland up to 15% in Egypt. Recently, Yao and colleagues did not find any survival benefit for the use of dual-loop diuretics over the use of a single loop diuretic. [69] The *Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan* (EVEREST) clinical trial showed that intensive diuretic therapy in-hospital or post-discharge was not associated with any rehospitalisation or mortality benefit, in comparison to the low dose of loop diuretic therapy. [67] The ESC guidelines recommend the use of two diuretics of different mechanisms of action. [1, 9]

The series of studies in this thesis found a disparity in the utilisation of MRA and MRA ≥ 50% target dose in Egypt and Ireland. This medication class had the highest prescription among all three guideline-directed medical therapies and greatest achievement of the recommended ≥ 50 % target dose in the CCU study of Egypt while its utilisation was low in both Irish studies (MUH and LTC studies). In Egypt, this high rate might be referred to the wide availability and affordable price of the combined furosemide-spironolactone product *'Lasilactone®'* in the Egyptian market. Also, its high utilisation is based on the additive diuretic effect of MRA and to decrease the number of daily tablets for enhanced patient's compliance and persistence. In Ireland, this underutilisation still represents a gap in knowledge similar to the European results as this underutilisation is seen in almost all European and American registries from 2011 till 2019. [86, 113, 196, 236] Savarese *et al.* enumerated some reasons for this underutilisation. The old age and chronic kidney disease might be the main reasons for the low utilisation despite the fact that MRA are not contraindicated in stable chronic kidney disease. Another potential reason was the omission of other HF medications such as RASi or EBBB that may lead to MRA omission. [113]

8.3.3 Potentially inappropriate prescribing in Heart Failure

In Ireland, the concurrent EBBB and non-dihydropyridine CCB combination is deemed high in the MUH data reflecting a need for questioning the prescribers about their perspective. In LTC facilities, there is room for preventing PIMHF items prescription and particularly NSAIDs. In Egypt, pregabalin was the driving PIMHF items even, after the introduction of clinical pharmacy services. The high PIMHF utilisation in all settings points to the need for a continued professional education intervention to increase prescriber's awareness about the harmful effects of PIMHF items and the alternative medication choices.

8.3.4 Impact on the existing Heart Failure literature of Ireland and Egypt

Overall, the last four thesis studies covered many gaps in knowledge that were identified in the narrative literature review of the thesis (Chapter 2). Chapter 4 represents the first assessment of HF prescribing practice in routine clinical practice in the absence of HF disease management programmes. Chapter 5 represents the first specific analysis of HF management in Irish LTC facilities. Chapter 6 represents the first comprehensive assessment of HF management in terms of patient's eligibility, consideration of contraindications and target dose achievement in Egypt. This is the first study of potentially inappropriate prescribing in Egypt regardless of the disease specificity. This study represents the first document for assessment of multidisciplinary care in Egypt and its feasibility for application in other low-medium income countries. Chapter 7 is the first document to address the barriers to guideline-led prescribing in Egypt and Middle-East.

8.4 Implications for policy, clinical practice and future research

8.4.1 Implications for policy

Clinical practice guidelines are important documents for guiding HF management and establishing benchmarks for quality of care. Optimal implementation of HF guidelines reduces healthcare costs associated with hospitalisation, prescription medicines, surgery, and other procedures. The economic benefit behind clinical guidelines can be the principal reason for promoting its implementation in healthcare settings. Also, the implementation of guidelines can prompt government or private payers to provide coverage or to reimburse doctors for evidence-based services. Clinicians may turn to clinical practice guidelines for medico-legal protection or reinforce their position in dealing with administrators who disagree with their

practice policies. A potential framework that may help in increasing the awareness and implementation of HF guideline-led prescribing is outlined in Table 8.2. [81, 272-275]

Secondly, this series of studies highlighted the adverse effect of multimorbidity and contraindications to therapies on HF prescribing quality despite the different income in each setting. This finding can represent a potential subject for leaders in HF research to address this gap in practice to increase the applicability and practicality of the clinical guidelines. Secondly, there is a vital need for better continued professional education for increasing awareness of the potentially inappropriate prescribing in HF.

The analysis of HF prescribing quality presented in Chapter 4 -6 is essential at the national level and could inform policy decisions. Another factor that could optimise the uptake of this research into policy is the publication of the systematic review (Chapter 3). This source of evidence has been suggested as a useful tool in policy development. [276]

8.4.2 Implication for practice

As a pharmacist, I am very much interested in empowering the role of pharmacists and particularly, clinical pharmacists in improving and optimising guideline-led prescribing and drug utilisation review. A meta-analysis of 12 randomised trials evaluating the effects of pharmacist's care on patient's outcomes in HF found that healthcare teams incorporating pharmacists reduced HF hospitalisations by 30% compared with usual routine care. [277] Chapter 4 was conducted in a setting with no pharmacist input and showed the phenomenon of clinical inertia as no patient achieved the 100% target dose of all three guideline-directed medical therapies. This implies a unique opportunity for the pharmacist to establish and run titration clinics. [207]

The current series of studies highlighted the use of some potentially inappropriate medications that impede or contradict the effect of guideline-directed medical therapies. These prescribing anomalies represent a potential room for clinical pharmacists to optimise HF prescribing practice. The ongoing PHARM-CHF (PHARMacy-based interdisciplinary program for patients with Chronic Heart Failure) randomised trial testing if team-based care with a pharmacist can improve medication management and adherence, provides more data on this promising intervention. [278]

Despite the high evidence to support the inclusion of clinical pharmacists in the multidisciplinary healthcare teams to reduce medications errors and improve the transition of care, it is evident that from our research that in both Ireland and Egypt, pharmacists still play a limited role in this regard. [84, 206, 207, 239, 261, 279-281] This can also be seen by the minor contribution of the clinical pharmacists in the Egyptian setting. In Egypt, the physician's fear of professional encroachment and the limited healthcare budget may represent barriers to more significant clinical pharmacy implementation. In Ireland, this limited role can be partly explained by the off-site location of community pharmacists, with limited opportunity to interact with LTC staff, outpatients clinics or primary care providers.

However, pharmacists first need to be up-skilled via further professional education in conducting academic detailing and the practicality of HF guideline-directed management. This was illustrated by one of the survey respondents as the need for well-trained and qualified clinical pharmacists (Chapter 7).

8.4.3 Implications for future research

In Ireland, studies about the benefit and contraindications of MRA prescribing is an important step. Also, an update of Chapter 4 regarding LTC prescribing quality is essential to compare the progression from 2010 to 2019.

In Egypt, qualitative research is needed to confirm some findings of the CCU survey (Chapter 7) and to explore barriers and misconceptions about EBBB prescription. Also, the dissemination of the current survey to a multi-centre study, including cardiology and primary care units, can provide a higher level of responses generalisability and policymaking. Next, a prospective study is necessary in the CCU setting in order to evaluate the acceptance rate and economic effectiveness of clinical pharmacists' interventions.

8.5 Strengths and limitations

One of the key strengths of the programme of research presented in this thesis is the "real-world" cohort study design. Randomised clinical trials (RCTs) are always highly selective and controlled studies. [71, 109] This may lead to a mismatch between the study populations of RCTs and the real-world patient population. [71, 256] Also, disease-management programmes are not affordable and applicable to all HF care settings in Ireland. Secondly, HF patients over 75 years or critically-ill patients are not represented in almost all RCTs; we conducted two studies specific to these vulnerable populations. [109] Thirdly, the comparative approach of this thesis demonstrated some differences in the prescribing perspectives between a developed country and a developing country of different cultures.

Some limitations must be acknowledged. First, the observational design of the studies has a lower evidence class than interventional studies in terms of causality relationship. However, this design aided us to review a larger number of patients charts and to study different healthcare settings in the two countries. Also, this design was helpful to perform a 5-year analysis in Egypt and a multicentre analysis in Ireland. Second, the single – centred design of Egypt based studies may present a limitation. However, this design was needed to study the details of HF prescribing practice in focused view and to elucidate the clinical reasoning of the prescribers in the same setting beyond prescribing practice. Thus, this design was helpful to have a full picture of HF prescribing practice in a leading clinical setting in Egypt. Also, it is important to consider the suboptimal availability and quality of patient charts data in the majority of other clinical settings in Egypt that would impede the accurate assessment of HF care.

Table 8.2 List of ideas to increase guideline adherence and implementation. [81, 272-275]

Category	Type	Description
Clinician support	Guideline summary	Short versions of Heart Failure guidelines for clinicians in print or electronic format including pocket cards, summaries, key messages or electronic reminders
	Algorithm	Flowcharts or clinical pathways that provide step-by-step guidance for patient management
	To-Do checklist	Print or electronic documents to be completed by clinicians for documentation in each patient medical record
Implementation support	Training material	Resources to support educational meetings or self-directed learning, such as PowerPoint presentations, educational modules, webinars or educational games.
	Resources	Human, infrastructure or funding resources, or instructions or processes needed for guideline implementation, e.g.: • Titration clinics: a patient-centric and comprehensive approach under the supervision of a clinical pharmacist to improve medication rational use and uptitration reduce the risk of adverse events, potentially inappropriate prescribing and improve medication adherence. • Coaching care teams on ways to identify high-risk patients lacking evidence-based services. • Linking Heart Failure care practices to regional health and drug information centres.
Evaluation support	Audit tools	Guidelines or manuals to evaluate and audit guideline-directed practice before and after guideline implementation.
	Measures	• Quality indicators or performance care measures by which to assess compliance with the guidelines' recommendations • Developing dashboards so clinicians can use data to manage patient care more effectively. Dashboards often provide at-a-glance views of key performance indicators relevant to a particular objective or business process. • Sending messages of commitment to excellence and quality.
	Feedback	Continuous and regular feedback on the prescribing performance and changes

8.6 Conclusion

Given the challenges of a growing older population with multiple comorbidities and who are frequently prescribed multiple drugs, healthcare professionals require effective, safe, and sustainable approaches to improve prescribing to HF patients. This thesis presents a comprehensive and detailed body of research on the contemporary prescribing practice to HF patients in the Irish and Egyptian routine clinical practice. At the end of this series of studies, one would expect a higher output of clinical pharmacy by greater empowerment of clinical pharmacy services in Ireland and broader implementation of services in Egypt in order to improve patient health outcomes and prevent adverse events. The thesis identified the need for locally-drafted guidance to make the international guidelines actionable and applicable for implementation in the Egyptian context; the need to introduce clinical pharmacy services in outpatient HF and LTC facilities in Ireland and the vital role of clinical pharmacists in acute and chronic HF care.

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Appendices

Appendix 1: St. Vincent's Potentially Inappropriate Medicines in Heart Failure (PIMHF) tool

1. Non-Steroidal Anti-Inflammatory Drugs
2. Cox-2 Inhibitors
3. Oral Corticosteroids
4. Decongestants
5. Non-Dihydropyridine Calcium Channel Blockers
6. Thiazolidinediones (-Glitazones)
7. Pregabalin
8. Metformin in Patients With Poor Renal Functions *
9. Oral Beta-2 Agonists
10. Itraconazole
11. Medicinal Formulations of High Sodium Content **

* Poor renal functions were defined as creatinine clearance lower than 50 millilitres per minute.[112]

** The medicinal formulations were defined based on the list of George *et al.* [282]

Appendix 2: The breakdown of the output of the systematic review search strategy.

Db	GAI	Guideline adherence index	Guideline adherence indicator	Global prescribing score	Quality circle	Guideline compliance	implementation of guidelines	guidelines implementation	strategies for guidelines implementation	process indicator	care indicator	appropriate prescribing	*Collective*	*Total*
PubMed	25	4	7	0	0	10	19	4	51	1	5	4	116	***246***
SCOPUS	13	4	8	0	0	13	32	7	0	0	4	11	0	***92***
WOK all databases	10	5	8	0	0	16	27	11	0	2	13	9	92	***193***
EmBase	54	5	12	0	0	18	38	15	0	4	7	21	155	***329***
Science Direct	252	1	2	0	1	108	195	28	0	25	49	105	762	***1528***
greylit.org	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
opengrey.eu	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
Academic Search Complete. CINAHL Psyinfo	12	2	4	0	0	9	12	6	0	1	5	2	2	***55***
Cochrane Library	1	1	1	0	0	1	2	2	0	2	1	0	0	***11***
Campbell Collaboration	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
	367	***22***	***42***	***0***	***1***	***175***	***325***	***73***	***51***	***35***	***84***	***152***	***1127***	***2454***

Abbreviations: WOK, Web of Knowledge

Appendix 3: The breakdown of the output of the updated systematic review search strategy (May 2016 – April 2019).

HEART FAILURE' AND	GAI	Guideline adherence index	Guideline adherence indicator	Global prescribing score	Quality circle	Guideline compliance	implementation of guidelines	guidelines implementation	strategies for guidelines implementation	process indicator	care indicator	appropriate prescribing	*Collective*	*Total*
PubMed	12	21	6	2	5	48	112	112	22	21	109	22	0	***492***
SCOPUS	6	25	14	2	2	319	0	139	0	0	231	22	0	***760***
WOK all databases	6	25	7	0	0	54	107	108	0	52	1	0	0	***360***
EmBase	25	4	3	0	0	8	8	1	0	0	0	5	3	***57***
greylit.org	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
opengrey.eu	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
Academic Search Complete. CINAHL Psyinfo*	-	-	-	-	-		-		-	-	-	-	-	**-**
Cochrane Library	0	1	10	4	0	1	1	1	0	5	5	0	0	***28***
Campbell Collaboration	0	0	0	0	0	0	0	0	0	0	0	0	0	***0***
	49	***76***	***40***	***8***	***7***	***434***	***228***	***361***	***22***	***78***	***346***	***49***	***3***	***1697***

**The research did not have access to the database due to its cost restriction. Abbreviations: WOK, Web of Knowledge*

Appendix 4: Letter from the Clinical Research Ethics Committee of the Cork Teaching Hospitals in respect of the study *Guideline-led prescribing to ambulatory Heart Failure patients in a cardiology outpatient service* (Chapter 4).

Tel: + 353 21 490 1001
Fax: + 353 21 490 1019

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (c) 12/04/15

4th March 2015

Dr Margaret Bermingham
Lecturer in Clinical Pharmacy
University College Cork
Room 1.27
Cavanagh Pharmacy Building
College Road
Cork

Re: Adherence to heart failure prescribing guidelines: a local and national observational study.

Dear Dr Bermingham

Expedited approval is granted to carry out the above study at:

- Mercy University Hospital and University College Cork.

The following documents have been approved:

- Signed Application Form
- Study Protocol
- CV for Chief Investigator
- Insurance Details.

We note that the co-investigators involved in this study will be:

- Mr Seif Yahia El Hadidi, PhD Student, Professor Stephen Byrne, Professor Carl Vaughan, Consultant Cardiologist and Professor David Kerins, Dept of Pharmacology and Therapeutics, UCC.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 5: Data Collection sheet used in the study *Guideline-led prescribing to ambulatory Heart Failure patients in a cardiology outpatient service* (Chapter 4).

Compilation Date: / /2016. ***R. ID*** ***M / F*** *Patient Name:* *DOB / /* *Conditions:* 1. 2. 3. 4. 5. 6. 7. 8. 9. 10. c. ***HF Dx site:*** ***Hospitalized?***	***Current Medications****: Loop - ACEI/ARBS – BBs – MRAs – Digoxin – Ivabradin ICD/CRT* ***Name / Dose /Frequency*** ***Prescriber*** ***Da***
Lab Investigations ***Smoker: Yes / No*** ***Ht=*** ***HR =*** ***BP=*** ***BNP=*** ***CHA2DS2-*** ***SOB – NYHA class=*** ***INR=*** ***SCr=*** ***Echo /20 EF=*** ***Echo /20 EF=***	

Appendix 6: Letter from the Research Ethics Committee, Faculty of Pharmacy and Pharmaceutical Sciences, Future University in Egypt in respect of the study *Guideline-led prescribing to heart failure patients at discharge from a critical care unit: the impact of a clinical pharmacy service* (Chapter 6).

FUTURE UNIVERSITY IN EGYPT
جامعة المستقبل

Research Ethics Committee
REC-FPSPI-FUE

Approval Form for Experimental Studies

Serial no. of the protocol: REC–FPSPI-9/56

Name of the researcher: Seif Yahia Salah El Hadidi

Title of the research PhD Thesis: Assessing heart failure prescribing quality among hospitalized patients in an Egyptian critical care setting and the barriers to guideline-led prescribing in hospitalized heart failure patients in Egypt.

Approval valid form: 11 / 10 / 2017

This is to certify that the research ethics committee for experimental and clinical studies at Faculty of Pharmacy, Future University, Cairo, Egypt has approved your research protocol.

Please be aware that study conduction will be mentioned by the REC.

Any changes in the study must receive review and approval prior to implementation unless the change is unnecessary for the safety of the experiment.

Chair of the Committee

Manal Kandeel

Prof. Dr. Manal M. Kandeel

Dean of Faculty of Pharmacy
Future University

Prof. Dr. Soham El Khashen

Research Ethics Committee
FPSPI

Appendix 7: Letter from the Research Ethics Committee, Faculty of Pharmacy and Pharmaceutical Sciences, Future University in Egypt in respect of the study *Factors Influencing Prescribing of Guideline-led Prescribing to Heart Failure Patients: a novel questionnaire in a critical care setting* (Chapter 7).

Approval Form for Experimental Studies

Serial no. of the protocol: REC-FPSPI-11/76

Name of the researcher: Seif Yahia Salah El Hadidi

Title of the research PhD thesis: Barriers to guideline-led prescribing among heart failure patients in Egypt: A survey to prescribers.

Approval valid form: 25 / 7 / 2018

This is to certify that the research ethics committee for experimental and clinical studies at Faculty of Pharmacy, Future University, Cairo, Egypt has approved your research protocol.

Please be aware that study conduction will be mentioned by the REC.

Any changes in the study must receive review and approval prior to implementation unless the change is unnecessary for the safety of the experiment.

Chair of the Committee

Prof. Dr. Manal M. Kendeel

Dean of Faculty of Pharmacy
Future University

8/8/2018

Prof. Dr. Seham El Kheshen

Research Ethics Committee
FPSPI

Appendix 8: Questionnaire used in Chapter 7: Factors influencing guideline-led prescribing to heart failure patients: a novel questionnaire in a critical care setting.

This survey was presented to respondents in hardcopy or on the Survey Monkey® website (www.surveymonkey.com)

Prescribing to heart failure patients in critical care: a survey of prescribers

Participant Information

Study title: Barriers to guideline-led prescribing among heart failure patients in Egypt: A survey to prescribers.

Purpose of the Study: The aim of this study is to assess the prescribing practice quality of doctors in a critical care unit in Egypt.

Who is carrying out the study: Dr. Naglaa Bazan – Head of Clinical Pharmacy Department in the Critical Care Unit – Cairo University. The other researchers involved in the study are:
- **Mr. Seif EL Hadidi, PhD scholar in the School of Pharmacy, UCC and FUE;**
- **Dr. Margaret Bermingham, Lecturer in Clinical Pharmacy, School of Pharmacy, UCC - Ireland;**
- **Prof. Ebtissam Darweesh, Chairman of Clinical Pharmacy Department, Faculty of Pharmacy, FUE - Egypt**
- **Prof. Stephen Byrne, Dean of School of Pharmacy, UCC - Ireland**

What will the study involve? The study will involve a questionnaire, which will obtain information on your opinion of the barriers to guideline-led prescribing in heart failure. The questionnaire will take around 10 minutes to complete. All survey replies will be anonymous.

Why have you been asked to take part?
1) You have been asked because you are practicing as prescriber in the critical care unit.
2) This survey will beneficially help to improve prescribing outcomes for heart failure patients.

Do you have to take part? No, participation is of course voluntary but we do hope you will participate and will value your input. Informed consent will be given by agreeing to complete this questionnaire online or on a hard copy. You may withdraw from the questionnaire at any time and for any reason. You may omit questionnaire items to which you do not wish to respond.

Will your participation in the study be kept confidential? Yes. Your participation will be confidential. You will not be asked to give your name or identifying information.

What will happen to the information which you give? The data will be kept confidential for the duration of the study, available only to me and my research supervisor. On completion of the study, they will be retained for a further ten years and then destroyed.

What will happen to the results? The results will be presented in a thesis. They will be seen by my supervisors, a second marker and an external examiner. The study may be published in a research journal and may inform the development of educational initiatives or communication materials around the care of patients with Heart Failure disease.

What are the possible disadvantages of taking part? There are no negative consequences envisaged for you in taking part.

What if there is a problem? In the event of any problem, please contact Dr. Naglaa Bazan (contact details below).

Who has reviewed this study (questionnaire)? The study was reviewed and approved by the Clinical Research Ethics Committee in Future University in Egypt.

Any further queries? If you need any further information about the study, you can contact Dr. Naglaa Bazan by phone: 02-23641459 or email: naglaabazan@yahoo.com.

If you have read the above information and wish to proceed with the questionnaire, click "OK".

1. What is your role:

- ○ Junior Resident Doctor
- ○ Senior Resident Doctor
- ○ Specialist
- ○ Consultant (for 0 – 5 years experience)
- ○ Consultant (for 6 – 10 years experience)
- ○ Consultant (for >10 years experience)

2. What information sources guide you for prescribing heart failure medicines? You may choose more than one option.

- ☐ My own clinical knowledge
- ☐ Hospital formulary
- ☐ Egyptian National Formulary (ENF)
- ☐ International clinical guidelines
- ☐ Other (please specify)
- ☐ International medical books (e.g. Kaplan & Oxford, … etc.)
- ☐ Facebook medical groups
- ☐ Informal Egyptian medical books such as (إمتيازولوجي – رشتولوجي)

3. The European Society of Cardiology published a new guideline on Acute and Chronic Heart Failure in 2016. Please rate your familiarity with this guideline using the scale below.

Completely unfamiliar	Unfamiliar	Neutral	Familiar	Very familiar
○	○	○	○	○

4. How often do you comply to the the 2016 European Society of Cardiology Guidelines on Acute and Chronic Heart Failure when prescribing to patients with heart failure? Please use the scale below.

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

5. When prescribing a loop diuretic to a heart failure patient to what extent do the following patient factors influence your prescribing choices?

	Never	Rarely	Sometimes	Often	Always
Age	○	○	○	○	○
Gender	○	○	○	○	○
Patient blood pressure	○	○	○	○	○
Patient heart rate	○	○	○	○	○
Patient renal function	○	○	○	○	○
Patient hepatic function	○	○	○	○	○
Patient pulmonary function	○	○	○	○	○
Patient potassium levels	○	○	○	○	○

Other (please specify)

6. When prescribing an ACE inhibitor or angiotensin receptor blocker or aldosterone antagonist to a heart failure patient to what extent do the following patient factors influence your prescribing choices?

	Never	Rarely	Sometimes	Often	Always
Age	○	○	○	○	○
Gender	○	○	○	○	○
Patient blood pressure	○	○	○	○	○
Patient heart rate	○	○	○	○	○
Patient renal function	○	○	○	○	○
Patient hepatic function	○	○	○	○	○
Patient pulmonary function	○	○	○	○	○
Patient potassium levels	○	○	○	○	○

Other (please specify)

7. When prescribing a beta-blocker to a heart failure patient to what extent do the following patient factors influence your prescribing choices?

	Never	Rarely	Sometimes	Often	Always
Age	○	○	○	○	○
Gender	○	○	○	○	○
Patient blood pressure	○	○	○	○	○
Patient heart rate	○	○	○	○	○
Patient renal function	○	○	○	○	○
Patient hepatic function	○	○	○	○	○
Patient pulmonary function	○	○	○	○	○
Patient potassium levels	○	○	○	○	○

Other (please specify)

8. Do you discuss medication choice with your heart failure patients? Please use the scale below.

Never	Rarely	Sometimes	Often	Always
○	○	○	○	○

9. To what extent do you consider each of the following issues to be a barrier or obstacle to prescribing guideline directed therapies in a heart failure patient? Please use the scale below.

	Never	Rarely	Sometimes	Often	Always
Lack of information for prescribers about the guidelines	○	○	○	○	○
Lack of Continuing Professional Development (CPD) resources on this topic	○	○	○	○	○
Lack of hospital guidelines	○	○	○	○	○
Lack of national guidelines	○	○	○	○	○
Personal lack of confidence in prescribing to heart failure patients	○	○	○	○	○
Medication shortages	○	○	○	○	○
Cost of medicine to hospital	○	○	○	○	○
Cost of medicine to patient	○	○	○	○	○
Work overload – lack of time	○	○	○	○	○
Physician information overload	○	○	○	○	○
Patient health literacy	○	○	○	○	○
Patient medication adherence	○	○	○	○	○

10. To what extent do you agree that each of the following actions would help you to improve heart failure prescribing outcomes? You may choose more than one option.

- ☐ Greater involvement of clinical pharmacist in care of heart failure patients.
- ☐ Clinical pharmacist providing education to prescribers about heart failure pharmacotherapy.
- ☐ Regular email updates to clinicians about heart failure medicines.
- ☐ Electronic notifications about appropriate prescribing for heart failure patients on hospital IT system.

11. Do you have any other comments about using heart failure prescribing guidelines in your practice?

Appendix 9: List of Postgraduate Training Modules and Academic Workshops

List of Postgraduate Training Modules

Definition of a postgraduate module

At UCC, a module represents a self-contained unit of a student's workload for the year and carries a unique examination/assessment mark. The size of a module is indicated by its credit weighting.

Module Record

Year	Module code	Module Name	ECTS (hour)	Module Aim
2016	**PG 6021**	English for Postgraduate Studies	5	To equip students whose first language is not English to successfully begin their postgraduate studies in English.
2016	**ST 6013**	Statistics and Data Analysis for Postgraduate Research Students	10	To provide an introduction to the statistical methods relevant to data analysis and practical applications of these methods.
2016	**PG 7021**	An Introduction to Ethics of Health Research	5	To examine the ethical issues which arise in the context of conducting clinical research involving human and animal participants
2017	**PG 6024**	Qualitative Research Inquiry	5	To facilitate postgraduate students to critically engage in philosophical and methodological debates around qualitative inquiry and to develop their knowledge and skills in the application of qualitative research methods.
2017	**PG 6015**	An Introduction to Research Integrity, Ethics and Open Science	5	To introduce students to the principles of responsible conduct in research and research data management and to the ethical considerations applying in specific disciplines.
2017	**PG 7016**	Systematic Reviews for the Health Sciences	5	To give postgraduate students an introduction to the principles and practice of systematic reviewing, as applied to their own PhD research To develop knowledge and understanding of systematic reviewing methods, applied to the quantitative and qualitative health research literature.
2019	**PG 7038**	Almost PhinisheD	5	To support students in the final write-up and submission stages and to develop the advanced doctoral student's professional profile. To develop personal effectiveness and career management skills as outlined in the UCC PhD Graduate Skills Statement.
2019	**PG 6003**	Teaching and Learning Module for Graduate Studies	5	To introduce graduates to the principles and practices of teaching and learning at the third level through engagement with teaching scenarios enacted through experiential learning and research informed teaching.
Total Credit hours			***45***	

Abbreviations: ECTS, European Credit Transfer System; PG, Postgraduate training module.

List of Academic Workshops

Workshop	Facilitator/Organiser
A clinical seminar about Pharmaco-epidemiology	Ass. Prof. Kathleen Bennett, Royal College of Surgeons in Ireland
Articulate Storyline & Video-scribe training workshop	Dr Eileen O'Leary, UCC Dr Suzanne McCarthy, UCC Patrick Kiely, UCC
Clinical Research Basic Skills workshop	Ronan Madden Assistant Librarian, UCC
Endnote reference manager workshop	Richard Bradfield, Liaison Librarian, UCC
How to Plan your PhD?	Prof. Hugh Kearns, Flinders University – Adelaide, Australia.
Information Literacy workshop	UCC medical library staff
Introduction of Drug Development & Good Clinical Practice for Investigation Medicinal Products training	UCC, Science Foundation Ireland and Royal College of Surgeons in Ireland
Master Poster design and presentation workshop	Dr Colman Casey, UCC Dr Teresa Barbosa, UCC Prof. Josephine Hegarty, UCC
One Day Writing for Publication Workshop www.grammatology.co.uk	Daniel Soule, UCC
Smoking Cessation workshop – Jigsaw educational technique	Dr Margaret Bermingham, UCC Ms Lisa Buckley, UCC
The seven secrets of Highly Successful Research Students	Prof. Hugh Kearns, Flinders University - Adelaide, Australia.
Turbocharge your Writing workshop	Prof. Hugh Kearns, Flinders University - Adelaide, Australia.
Two-Day Short Course Introductory to Intermediate SPSS	Dr Kathleen O'Sullivan, UCC
Writing a Good research paper workshop	Prof. Ivan Perry, UCC
Writing Clinics	UCC Student Skills Center

Appendix 10: UCC Travel Bursaries

The Graduate School in the College of Medicine and Health at UCC awards 10 Travel Bursaries of €1,000 each for students currently registered for a doctoral degree in the College of Medicine and Health.

The purpose of these awards is twofold:

- To facilitate students who wish to present their work at an international conference.
- To facilitate the training of students who wish to acquire skills that are essential for their academic development, but which they cannot otherwise receive in UCC.

UCC Travel Bursary for attending ESC Heart Failure Congress, Paris 2017

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Seif Yahia Salah El Hadidi <114220546@umail.ucc.ie>

Graduate School: Travel Bursary 2016-17

1 message

Graduate School, Medicine and Health <gradschoolmh@ucc.ie> 4 October 2016 at 15:12
To: Seif Yahia Salah El Hadidi <114220546@umail.ucc.ie>

4th October 2016

Seif Yahia Salah El Hadidi

Dear Seif,

On behalf of the College of Medicine and Health, I am delighted to inform you that you have been awarded a College of Medicine and Health doctoral student travel bursary subject to your abstract being accepted for presentation at the conference.

The general purpose of these awards are twofold:

1. To facilitate students in obtaining training in support of their academic development which they cannot otherwise receive in UCC.
2. To facilitate students to attend and present at an international conference.

You have been awarded a bursary which covers the expenses to the maximum amount as outlined in your application. Expenditure will be reimbursed to each student on the basis of a fully vouched expenses claim and receipt of a report (Appendix 1) within one month of travel.

UCC Travel Bursary for attending ESC Heart Failure Congress, Athens 2019

UCC
University College Cork, Ireland

College of Medicine and Health
GRADUATE SCHOOL

1st November 2018

Dear Seif,

On behalf of the College of Medicine and Health I am delighted to inform you that you have been awarded a College of Medicine and Health doctoral student travel bursary.

The general purpose of these awards are twofold:

1. To facilitate students in obtaining training in support of their academic development which they cannot otherwise receive in UCC.
2. To facilitate students to attend and present at an international conference.

You have been awarded a bursary which covers the expenses to the maximum amount as outlined in your application, €1,000. Expenditure will be reimbursed to each student on the basis of a fully vouched expense claim and receipt of a report (Appendix 1) within one month of travel. Students who are attending a conference will also have to present evidence of presenting (oral or poster presentation) at the pertinent conference. Students attending training courses must supply evidence of having attended the course (as outlined in their application).

I would like to take this opportunity to wish you well with your doctoral studies.

Yours sincerely,

Professor Eileen Savage PhD MEd BNS RGN RCN
Vice Dean Graduate Studies
College of Medicine and Health, UCC

CC Jane Hurley, Executive Assistant, Graduate School College of Medicine and Health