Delayed left ventricular remodelling and optimal medical therapy in patients with heart failure with reduced ejection fraction. A systematic review

Laurence William Whittaker

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The University of Hull and The University of York

Hull York Medical School

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Abstract

Introduction

International guidelines recommend implantable cardioverter-defibrillators (ICDs) for patients with heart failure and a reduced ejection fraction (HFrEF) to reduce the risk of sudden cardiac death (SCD) if patient's left ventricular ejection fraction (LVEF) remains 35% or less despite three months of optimal medical therapy (OMT). However, more efficacious OMT has become available since the pivotal ICD trials were published, and recent studies have reported improvements in LVEF with OMT beyond three months.

Objective

To report LVEF improvement and mortality in patients with HFrEF that were eligible for primary prevention ICDs.

Methods

A systematic review and narrative synthesis of studies examining patients with HFrEF who had an LVEF of 35% or less after at least three months of OMT, and who were treated with a longer duration of OMT.

Results

Fourteen studies met the eligibility criteria. All 14 studies included patients with HFrEF that were prescribed sacubitril/valsartan because their LVEF remained 35% or less despite at least three months of OMT. Three studies reported the temporal change in ICD eligibility, reporting that between 21% and 25% of patients were no longer considered eligible for a primary prevention ICD after six months, which increased to around 40% after 12 months. Six studies reported mortality, which varied from 0% to 7.6% during follow-up (between six and 24 months). No studies reported SCD distinct from all-cause mortality.

Conclusion

In a large proportion of patients with HFrEF, an increase in LVEF to more than 35% was observed with longer duration OMT. Thus, ICD implantation may be avoidable for many patients if decision-making was delayed until patients have been prescribed OMT for longer. However, the included studies lacked data on the mode of death in patients with HFrEF. This is an important consideration for potentially delaying ICD implantation and should be the focus of future work.

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Author's declaration

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Chapter 1: Introduction

1.1 Heart failure - background

Heart failure is a common medical problem, affecting 1-2% of people in Europe and North America(1). It is a clinical syndrome defined by the presence of key symptoms (e.g., breathlessness and fatigue) with or without clinical signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema). The causes of heart failure can be divided into myocardial disease, valvular disease, pericardial disease, arrhythmias, congenital heart disease and high output states(2). Most of these pathologies cause heart failure due to either systolic or diastolic left ventricular dysfunction(3). Heart failure secondary to isolated right ventricular dysfunction will not be discussed in this thesis and any subsequent reference to systolic or diastolic dysfunction will refer to left ventricular dysfunction unless otherwise stated. Systolic dysfunction refers to impairment during ventricular contraction (systole) whereas diastolic dysfunction refers to impairment during ventricular relaxation and filling (diastole)(4, 5). In practice, heart failure is often categorised according to the left ventricular ejection fraction (LVEF), which is one measure of systolic function(4). LVEF refers to the relative size of the stroke volume (volume 'ejected' with each contraction) compared to the end diastolic volume (maximum ventricular volume)(4). The commonest imaging modality for assessing LVEF is transthoracic echocardiography (TTE), but other modalities including transoesophageal echocardiography (TOE), magnetic resonance imaging (MRI) and nuclear imaging techniques are also used(3).

The prevalence of heart failure increases with age, with estimates in the United Kingdom (UK) ranging from between one in 35 adults aged 65 to 74 years old, rising to one in seven adults aged over 85(2). Symptoms are typically classified using the New York Heart Association (NYHA) scale, which ranges from one (no symptoms) to four (symptoms at rest or with minimal exertion)(3).

Treatment costs for heart failure are high, with 1% to 2% of European and North American healthcare budgets spent on heart failure each year(1). Part of the high cost is attributable to hospitalisation, which is often prolonged. In the UK, the National Heart Failure Audit (NHFA) recorded nearly 70,000 hospital admissions for heart failure in 2019/20(6), the latest

complete dataset prior to the Covid-19 pandemic. The median length of stay was nine days for patients that were managed on a cardiology ward(6). The same audit reported in-hospital mortality rates of 9%, and one year mortality rates of 34%(6). European registry data shows a similarly poor prognosis, with one year mortality rates of 25.9%(7). Furthermore, in this same European registry, 26.7% of patients hospitalised for heart failure were readmitted to hospital during the first year following discharge(7). The prevalence of heart failure is expected to increase over time due to an ageing population and overall population growth(3). Additionally, the prevalence of significant co-morbid conditions in heart failure patients is growing, which further adds to the cost and complexity of treating these patients(3).

1.1.1 Heart failure with reduced ejection fraction (HFrEF)

In the UK, around 50% of patients with heart failure have left ventricular systolic dysfunction (LVSD)(8). As stated, systolic function is commonly quantified using the LVEF(3). According to the LVEF, LVSD may be categorised by severity, although exact LVEF cut-points and terminology varies between guidelines (table 1)(3, 8, 9). In practice, the terms severe LVSD and heart failure with reduced ejection fraction (HFrEF) are often used interchangeably. However, LVSD refers to systolic function as measured by an imaging test, whereas HFrEF usually refers to the presence of heart failure symptoms in addition to LVSD (table 1).

Table 1: LVEF ranges and terminology in different guidelines (adapted from BSE, ESC and NICE guidelines)

Society/guideline	Categories	LVEF ranges/thresholds (%)
British Society of Echocardiography (BSE) (2020)(9)	Normal	≥55
	Borderline reduced	50-54
	Impaired	36-49
	Severely impaired (severe LVSD)	≤35
European Society of Cardiology (ESC) (2021)(3)	Preserved	≥50
	Mildly reduced	41-49
	Reduced (HFrEF)	≤40
National Institute for Health and Care Excellence (2018)(8)	Preserved	>40
	Reduced (HFrEF)	≤40

HFrEF - heart failure with reduced ejection fraction, LVEF - left ventricular ejection fraction, LVSD - left ventricular systolic dysfunction

Patients with HFrEF have the highest risk of mortality compared to other categories of heart failure(10), and it is in this group that the majority of prognostically important heart failure treatments have been developed(3). The treatment aims for patients with heart failure are to reduce mortality, reduce heart failure hospital admissions, and improve symptoms and quality of life(3). Current management options for HFrEF include medications and implantable cardiac devices, which will each be discussed in turn.

1.2 Optimal medical therapy (OMT)

Initial treatment for HFrEF is pharmacological with a combination of medications. The timings and specific medications used vary between guidelines (figures 1 and 2), but can broadly be divided into four groups:

1. Renin-angiotensin system (RAS) inhibition, comprising angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-receptor blockers (ARB) and combined angiotensin-receptor blocker/neprilysin inhibitors (ARNI)

2. Beta-blockers

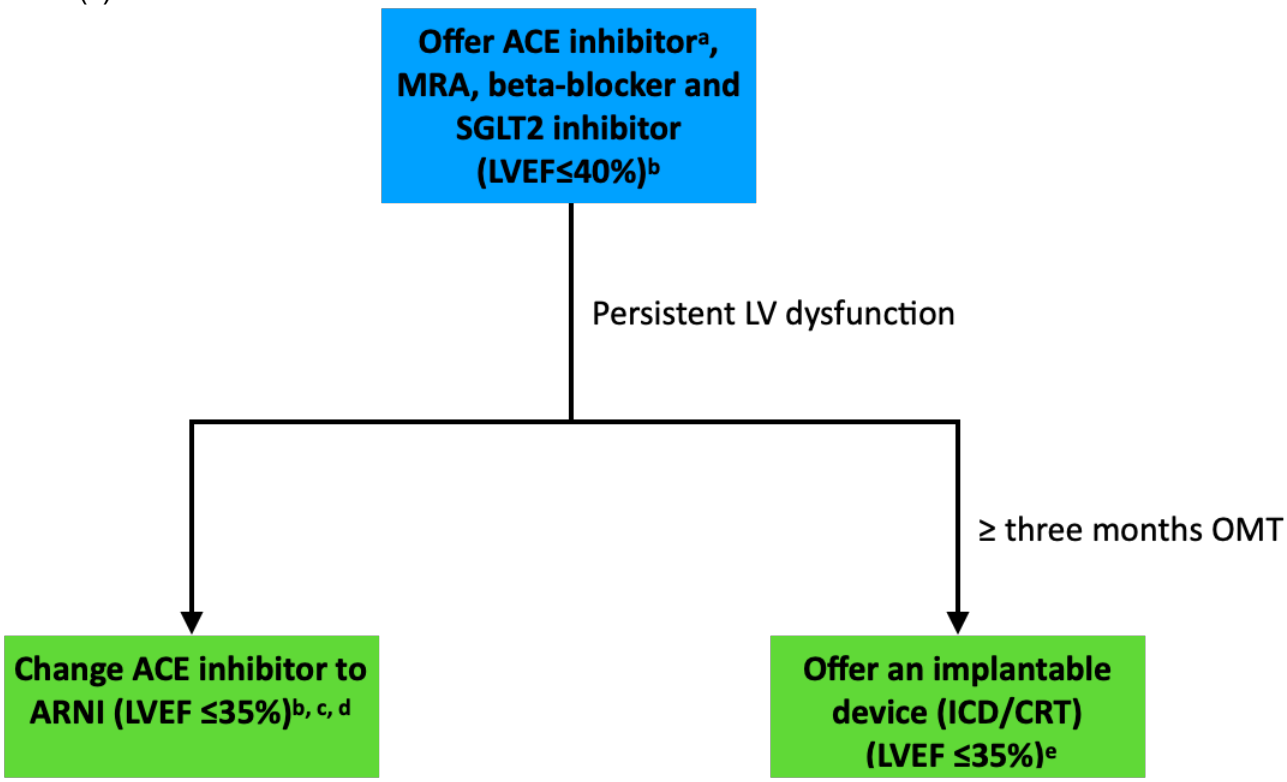
3. Mineralocorticoid receptor antagonists (MRA)

4. Sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors).

Each of these therapies reduce the risk of mortality and heart failure hospitalisation(3, 11). Optimal medical therapy (OMT) is defined as the maximally tolerated doses of two to four of these medications depending on the guideline and patient response to initial treatment (figures 1 and 2).

However, despite advances in care, mortality and morbidity for patients with HFrEF remains high, especially following a hospital admission for heart failure(7). Complex implantable cardiac devices are an additional treatment option for patients with HFrEF who do not respond to initial pharmacological treatment. Complex devices include implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT). The eligibility criteria and timing of implantation for complex devices vary between guidelines (figures 1 and 2, tables 3 and 4)(3, 12). This will be discussed in more detail later, but, in broad terms, they are offered to patients with HFrEF whose LVEF remains severely reduced despite a period of optimal medical therapy(3, 12). The evidence and recommendations for complex devices will be considered in turn.

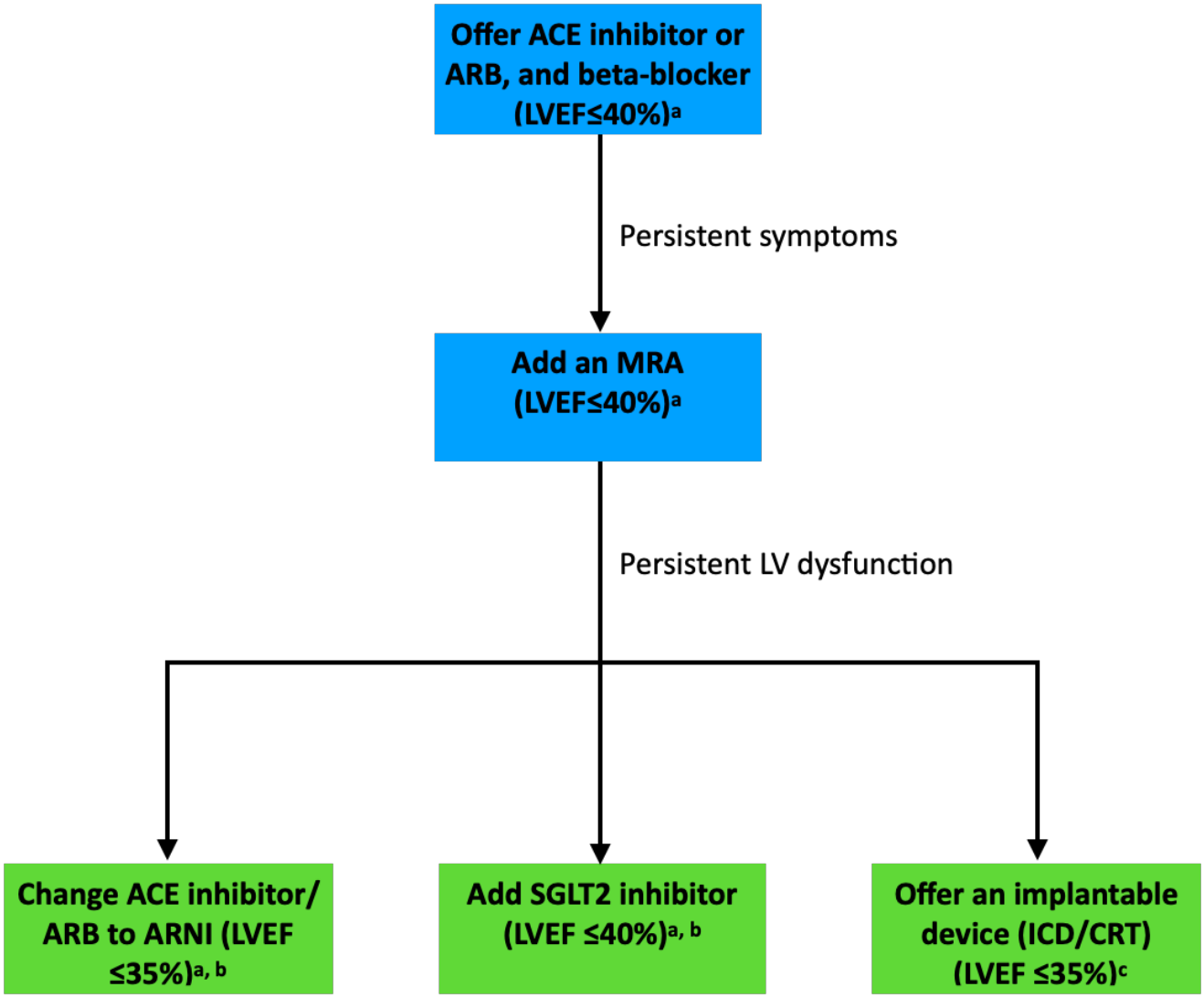
Figure 1: Optimal medical therapy pathway adapted from ESC guidelines for patients with HFrEF(3)



a ARNI may be considered first line instead of ACE inhibitor (Class IIb evidence - "usefulness/efficacy is less well established by evidence/opinion")
b Titrate to maximum tolerated dose
c If NYHA II-IV symptoms
d Change to ARB if ACEi and ARNI not tolerated
e Device choice based on QRS duration and NYHA class (see table 3)

ACE - angiotensin converting enzyme, ARB - angiotensin receptor blocker, ARNI - angiotensin receptor blocker/neprilysin inhibitor, CRT - cardiac resynchronisation therapy, ESC - European Society of Cardiology, ICD - implantable cardioverter-defibrillator, LVEF - left ventricular ejection fraction, MRA - mineralocorticoid receptor antagonist, NYHA - New York Heart Association, SGLT2 - sodium-glucose co-transporter 2

Figure 2: Optimal medical therapy pathway adapted from NICE guidelines for patients with HFrEF(8)



a Titrate to maximum tolerated dose

b If NYHA II-IV symptoms

c Device choice based on QRS duration and NYHA class (table 4)

ACE - angiotensin converting enzyme, ARB - angiotensin receptor blocker, ARNI - angiotensin receptor blocker/neprilysin inhibitor, CRT - cardiac resynchronisation therapy, ICD - implantable cardioverter-defibrillator, LVEF - left ventricular ejection fraction, MRA - mineralocorticoid receptor antagonist, NICE - National Institute for Health and Care Excellence, NYHA - New York Heart Association, SGLT2 - sodium-glucose co-transporter 2

1.3 Prognostic factors in HFrEF

Several factors are associated with a poor prognosis in patients with heart failure. As already stated, patients with HFrEF have a higher risk of mortality compared to patients with other forms of heart failure(10). Within HFrEF, a lower EF is also associated with poorer prognosis, with the composite outcome of death and heart failure hospitalisation increasing by 13% for every 5% reduction in LVEF below 45%(13). Other significant prognostic factors include age, with each decade over 60 years old associated with a 46% increase in the composite outcome of death or heart failure hospitalisation(13). Factors which are also associated with poorer outcomes, albeit to a lesser extent, include NYHA class, atrial fibrillation (AF), mitral regurgitation, ischaemic heart disease (IHD), renal dysfunction and N-terminal pro-B type natriuretic peptide levels (NT-proBNP)(3, 13, 14).

Whilst the ESC and NICE guidelines recommend up-titration of heart failure medications to the maximally tolerated doses(3, 8), there is mixed data with regards to drug doses and prognosis. The ATLAS trial for the ACE inhibitor lisinopril, and the HEAAL trial for the ARB losartan, both found lower rates of heart failure hospitalisation in patients on higher drug doses(15, 16). Conversely, for beta blockers, MRA and ARNI no such association has been demonstrated(17, 18). However, several authors have noted an trend towards poorer outcomes in patients for whom doses of ACE inhibitors, ARB and ARNI are reduced(19, 20). Risk factors for dose reduction include age, renal dysfunction and systolic blood pressure less than 120mmHg(19, 20).

1.4 Complex implantable devices

As outlined in figures 1 and 2 (see section 1.2), complex implantable devices may be considered for patients with HFrEF, if they do not respond to initial medical treatment(3, 8). Complex implantable devices include both implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) devices. Each of these will now be discussed in turn.

1.4.1 Implantable cardioverter-defibrillators

The risk of sudden cardiac death (SCD), as a result of ventricular arrhythmias (ventricular fibrillation – [VF], and ventricular tachycardia – [VT]), is increased in patients with heart

failure compared to the general population, with the highest risk in patients with HFrEF(12). ICDs may be used to reduce the risk of SCD(12).

1.4.1.1 History and development

The first ICD implant in a human was performed in 1980 and involved the placement of an epicardial lead via a thoracotomy(21). The early devices were basic, as they were only able to detect and deliver shocks for ventricular fibrillation(21). Since this pioneering work, several advances have been made. Transvenous endocardial leads have been developed and refined(22, 23). More recently, subcutaneous ICDs (S-ICD) have been developed, which obviate the need for an epicardial or endocardial lead(24). Device programming is also increasingly sophisticated. Since the early 1990s, devices have been capable of detecting VT in addition to VF. Devices with epicardial or endocardial leads also have the capacity to deliver anti-tachycardia pacing (ATP) as an alternative to shocks to terminate VT(25). Further refinements include algorithms and programming strategies to reduce shock rates, whilst also reducing mortality(26-28). However, there remain significant risks associated with an ICD implant regardless of the device used. Estimated procedural risk in one meta-analysis of transvenous ICD implants was 9.1%, with varying contributions from lead displacement, pneumothorax, haematoma and infection(29). Similar complication rates have been found in registry data for S-ICDs(30). Aside from the implant-associated risks, there is also a 2-3% risk per year of inappropriate shocks (shocks delivered for supraventricular arrhythmias or due to device malfunction)(26, 28, 31, 32, 32).

Out with the acute procedural risks, having an ICD may impact negatively on patients. Post-procedure pain, both from the surgical wound and from limitations on use of the ipsilateral arm, have been reported in several studies(33). This pain can take weeks or months to dissipate(33). Additionally, fear and anxiety, particularly regarding anticipated shocks, are also frequently reported(33). This anxiety is further heightened following a shock, regardless of whether the shock was appropriate or inappropriate(34). Furthermore, receiving a shock negatively impacts on a patient's activity levels for up to 90 days, regardless of whether the patient is hospitalised(34). There is also evidence of higher mortality following ICD therapy. One meta-analysis found a higher mortality following ICD shocks for both appropriate and

inappropriate shocks(35).

The indications for ICDs in patients with HFrEF are divided into primary and secondary prevention. Primary prevention is where an implant is offered to patients who have not experienced a life-threatening ventricular arrhythmia but are at increased risk compared to the baseline population. As already discussed, patients with HFrEF are at risk of VT and VF(12). Secondary prevention is where an implant is offered to patients who have survived a life-threatening ventricular arrhythmia(12). Secondary prevention ICDs will not be discussed further in this thesis.

1.4.1.2 Evidence in primary prevention

The evidence for offering primary prevention ICDs to patients with HFrEF comes primarily from the MADIT II (2002)(36), SCD-HeFT (2005)(37) and DANISH (2016)(38) trials. Several other primary prevention ICD trials have been performed and are presented in table 2 for completeness as these trials were considered by the ESC(3) and NICE(12) guideline committees as part of their appraisal of the evidence. However, as these trials were small compared to MADIT II, SCD-HeFT and DANISH, and they found no significant difference in all-cause mortality between their respective ICD groups and control groups(39-41) they will not be discussed in further detail in this thesis.

MADIT II randomised patients with ischaemic heart disease and HFrEF (defined as LVEF less than or equal to 30%) to either usual medical care or usual medical care plus an ICD(36). The mean follow-up was 20 months. All-cause mortality was significantly lower in the ICD group (14.2% vs 19.8%)(36). This was primarily driven by a difference in SCD rates (3.8% vs 10.0%)(42). In SCD-HeFT, patients with HFrEF (defined as LVEF of 35% or less) of any aetiology were randomised to either usual medical care, usual medical care plus an ICD, or usual medical care plus the anti-arrhythmic drug amiodarone(37). Median follow-up was 45.5 months. As with MADIT II, all-cause mortality was also significantly lower in the ICD group compared to usual medical care (22% vs 29%), with overall higher mortality likely reflecting longer follow-up duration in SCD-HeFT(37). As with MADIT II, the difference in all-cause mortality was driven primarily by a difference in SCD rates (4.5% vs 11.2%)(43). All-

cause mortality rates in the ICD group and amiodarone group were not significantly different. DANISH randomised patients with non-ischaemic cardiomyopathy to either usual medical care or usual medical care plus an ICD(38). The mean follow-up was 29 months. The difference in all-cause mortality between the two groups was not statistically significant (21.6% vs 23.4%), though the difference in rates of sudden-cardiac death was statistically significant (4.3% vs 8.2%)(38).

Table 2 - selected primary prevention ICD trials

Trial	**n**	**Heart failure aetiology**	**Treatment groups**	**Follow-up duration**	**All cause mortality, n (%)**		**SCD, n (%)**	
					ICD	Control	ICD	Control
CAT (2002)(39)	104	Dilated cardiomyopathy	ICD vs OMT	5.5 years (SD 2.2)	13 (26)[a]	17 (31)[a]	0[b]	0[b]
MADIT II 2002(36, 42)	1232	IHD	ICD vs OMT	20 months (range 0.2-56)	105 (14.2)	97 (19.8)	28 (3.8)	49 (10.0)
AMIOVIRT (2003)(40)	103	Non-ischaemic	ICD vs Amiodarone	2.0 years (SD 1.3)	7 (11.8)[a]	6 (13.5)[a]	1 (2.0)[a]	2 (3.8)[a]
DEFINITE (2004)(41)	458	Non-ischaemic	ICD vs OMT	29.0 months (SD 14.4)	28 (12.2)[a]	40 (17.5)[a]	3 (1.3)	14 (6.1)
SCD-HeFT 2005(37, 43)	2521	Any	ICD vs OMT vs Amiodarone	45.5 months	182 (22.0)	244 (28.8)[c]	37 (4.5)	95 (11.2)[c]
DANISH 2016(38)	1116	Non-ischaemic	ICD vs OMT	67.6 (IQR 49-85)	120 (21.6)[a]	131 (23.4)[a]	24 (4.3)	46 (8.2)

[a] *Not statistically significant*

[b] *Only reported after one year of follow-up. SCD separate to all-cause mortality at the end of follow-up not reported*

[c] *OMT group*

ICD - implantable cardioverter-defibrillator, IQR - interquartile range, OMT - optimal medical therapy, SCD - sudden cardiac death, SD - standard deviation

1.4.2 Cardiac resynchronisation therapy

QRS prolongation on a surface electrocardiogram (ECG) is associated with increased mortality in patients with HFrEF independent of age, aetiology of heart failure and severity of symptoms(44). QRS prolongation is common in HFrEF, affecting between 25% and 50% of patients(31). Left bundle branch block (LBBB) is one cause of QRS prolongation and is also common in HFrEF, affecting between 15% and 27% of patients(31). LBBB results from either damage to cardiac conduction tissue and/or altered electrical properties within areas of heart muscle(45). It is a marker of either interventricular (between right and left ventricles) and/or LV intraventricular (within the left ventricle) dyssynchrony (45). PR prolongation, the manifestation of atrioventricular (AV) delay (occurring between the atria and the ventricles), is also common in HFrEF(31). In diastole, dyssynchrony causes suboptimal LV filling(46). In systole, dyssynchrony increases myocardial work, reduces LV contractility and increases mitral regurgitation(46). The result is worsening LV systolic function(46). Dyssynchrony also increases the risk of VT and VF(46). CRT aims to reverse this process by correcting atrioventricular, interventricular and LV intraventricular dyssynchrony(31).

CRT devices typically comprise three leads (or two leads in patients with permanent atrial fibrillation), one for each of the right atrium, right ventricle and left ventricle. CRT devices can either include purely pacemaker function (termed CRT pacemaker or CRT-P) or incorporate a cardioverter-defibrillator function in addition (termed CRT defibrillator or CRT-D), depending on whether a purely pacing or a combined pacing/defibrillator lead is used in the right ventricle. The main difference between CRT and other implanted cardiac devices is the presence of a pacing lead for the left ventricle. This is most frequently placed transvenously in a branch of the coronary sinus, though leads may also be placed epicardially(31). Alternative methods of left ventricular pacing, either using an endocardial LV lead or via conduction system pacing are the subject of ongoing clinical trials(47, 48). Implanting a CRT device requires a surgical procedure, like a transvenous ICD. However, the additional (LV) lead adds procedural time and complexity, and thus procedural risk is higher than ICDs(49).

In selected patients with HFrEF, CRT reduces both mortality(50, 51) and heart failure hospitalisation(50-53). CRT also causes LV reverse remodelling(50, 54). Patients with LBBB, a

QRS duration of 150ms or more and sinus rhythm are most likely to benefit from CRT(31).

1.4.3 Current implantable device guidelines

The 2021 ESC guidelines recommend that a primary prevention ICD is offered to patients with HFrEF if their left ventricular systolic function remains severely impaired despite three months of OMT, and the patient has NYHA class two or three symptoms (table 3)(3). Prior to the publication of the DANISH trial(38), the ESC guidelines gave the same class I recommendation for primary prevention ICD implantation irrespective of the aetiology of heart failure(55). A class I recommendation means that in the opinion of the guideline committee "evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective." However, based primarily on the data from DANISH, in the updated 2021 ESC guidelines(3) the recommendation for primary prevention ICD implantation in patients with a non-ischaemic aetiology was changed to class IIa ("conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure, [though] weight of evidence/opinion is in favour of usefulness/efficacy"). The NICE guidelines have not been updated since the publication of DANISH, so their ICD recommendations are the same irrespective of heart failure aetiology(12). Persistent severe LVSD despite three months of OMT was an inclusion criterion in the SCD-HeFT trial and has been incorporated into the ESC guidelines(3, 37). Separate recommendations were made regarding the use of CRT, which is largely determined by QRS duration and the presence of LBBB (table 3). The 2014 NICE guidelines make similar recommendations (table 4), though no specific recommendations were made regarding the minimum duration of OMT required prior to considering a complex device(12).

Table 3: Complex device guidelines adapted from 2021 ESC guidelines(3)

	NYHA class			
QRS interval (milliseconds)	**I**	**II**	**III**	**IV**
<130ms	ICD and CRT not indicated	ICD	ICD	ICD and CRT not indicated
130-149ms without LBBB	ICD and CRT not indicated	CRT-P/D[a] or ICD	CRT-P/D[a] or ICD	CRT-P[a]
130-149ms with LBBB	ICD and CRT not indicated	CRT-P/D	CRT-P/D	CRT-P
≥150ms with or without LBBB	ICD and CRT not indicated	CRT-P/D	CRT-P/D	CRT-P

a - May be considered

CRT - cardiac resynchronisation therapy, ESC - European Society of Cardiology, ICD - implantable cardioverter-defibrillator, LBBB - left bundle branch block, NYHA - New York Heart Association

Table 4: Complex device guidelines adapted from 2014 NICE guidelines(8)

	NYHA class			
QRS interval (milliseconds)	**I**	**II**	**III**	**IV**
<120ms	ICD	ICD	ICD	ICD and CRT not indicated
120-149ms without LBBB	ICD	ICD	ICD	CRT-P
120-149ms with LBBB	ICD	CRT-D	CRT-P/D	CRT-P
≥150ms with or without LBBB	CRT-D	CRT-D	CRT-P/D	CRT-P

CRT - cardiac resynchronisation therapy, ICD - implantable cardioverter-defibrillator, LBBB - left bundle branch block, NICE - National Institute for Health and Care Excellence, NYHA - New York Heart Association

1.4.4 Cost-effectiveness

Cost-effectiveness assessments for complex implantable devices inform the recommendations for their use by NICE in the UK. NICE's preferred measure for cost-effectiveness is cost per quality-adjusted life year (QALY). Generally, a cost of £20,000 to £30,000 per QALY is accepted as cost-effective(56). The estimated cost per QALY for complex devices varies by device type (ICD, CRT-P or CRT-D) and by patient characteristics (NYHA class, QRS duration) ranging from £10,494 to £28,646 per QALY(12). However, the cost-effectiveness data used is based on a systematic review of trials up to 2012(57). Lower mortality in heart failure patients has been observed in more recent trials, which may impact on the cost utility analysis(58). This is particularly relevant for ICDs, as their only benefit is a reduction in SCD. If the risk of SCD is lower, a greater number of patients will need to receive an ICD for the same increase in QALY.

1.5 Challenging the current guidelines

1.5.1 Changing definitions of OMT

As discussed in section 1.4.1.2, current NICE recommendations for primary prevention ICDs are primarily based on data from MADIT II (2002)(36) and SCD-HeFT (2005)(37), with the ESC also incorporating data from DANISH (2016)(38) in their recommendations. However, there are issues with applying the results of MADIT II and SCD-HeFT to our current HFrEF population. MADIT II and SCD-HeFT were published at a time when medical therapy for HFrEF was largely limited to ACE inhibitors, ARBs and beta-blockers, with MRAs only available during the latter stages of SCD-HeFT. Contemporary OMT has developed over many years, with new medications added following the publication of key clinical trials (table 6, section 1.5.3.1). As discussed in section 1.2, current OMT comprises a combination of four medications titrated to maximally tolerated doses: an ACE inhibitor (or ARB, or the newer ARNI), a beta-blocker, an MRA and an SGLT-2 inhibitor. However, even for the limited number of medications available at the time, prescribing rates of heart failure therapies were sub-optimal in these trials. In MADIT II, only 70% of patients were prescribed an ACE inhibitor and/or beta-blocker. In SCD-HeFT, 96% were prescribed an ACE inhibitor or ARB, though only 69% of patients were prescribed a beta-blocker. Only 19% were

prescribed an MRA, though the pivotal trial for this class of drug was only published in the latter stages of SCD-HeFT(59). In DANISH, the rates of OMT were higher than MADIT II and SCD-HeFT, with 96% of patients prescribed an ACE inhibitor, 92% of patients prescribed a beta-blocker and 58% of patients prescribed an MRA. However, both ARNI and SGLT2 inhibitors were unavailable in MADIT II, SCD-HeFT and DANISH as these drugs were only licensed later (table 6, section 1.5.3.1).

Current NICE recommendations for CRT are based primarily on data from the MUSTIC (2001)(60), MIRACLE ICD (2003)(61), COMPANION (2004)(62) and CARE-HF (2005)(57) trials. The current ESC guidelines additionally use data from the REVERSE (2008)(54), MADIT-CRT (2009)(63) and RAFT (2010)(51) trials. As with the pivotal ICD trials, prescribing rates of heart failure therapies were often sub-optimal in the key CRT trials. Prescribing rates of medical therapy did generally increase with the trial publication date, from 89% prescribed an ACE inhibitor or ARB and 58% prescribed a beta-blocker in MIRACLE ICD, to 97% prescribed an ACE inhibitor or ARB, 90% prescribed a beta-blocker and 42% prescribed an MRA in RAFT. However, as with the key ICD trials, neither ARNI nor SGLT2 inhibitors were available during any of these CRT trials.

More recent trials challenge our current approach to complex device implantation. PARADIGM-HF (2014)(64) demonstrated reduced mortality and heart failure hospitalisation in patients randomised to sacubitril/valsartan (an ARNI), compared to the control group who continued an ACE inhibitor. DAPA-HF (2019)(65) demonstrated reduced heart failure hospitalisation in patients randomised to dapagliflozin (an SGLT2 inhibitor) in addition to existing OMT, compared to the control group who continued existing OMT alone. Additionally, a later analysis of DAPA-HF data found a reduction in SCD in the dapagliflozin group(66). Lower rates of heart failure hospitalisation with contemporary OMT may reduce the effectiveness of CRT, and lower cardiac mortality may reduce the effectiveness of both CRT and ICDs. Declining SCD rates with newer medications is particularly relevant for ICDs, which have no other role in patients with HFrEF.

1.5.2 Delayed remodelling

A further reason to reconsider our current complex implantable device pathways is delayed LV reverse remodelling. There is a degree of heterogeneity in the literature regarding the definition of LV reverse remodelling, but in its broadest terms it simply refers to an improvement in LV systolic and diastolic function secondary to improvement/normalisation of LV volumes and shape(67). For primary prevention ICDs, LV reverse remodelling is relevant as such devices are only indicated if LVEF remains 35% or less despite medical therapy(3, 12). However, the timing of LV reverse remodelling is also important. Whilst the ESC guidelines recommend a minimum of three months of OMT prior to considering a complex device(3), several authors have highlighted variability in the timing of LV reverse remodelling in patients with HFrEF prescribed medical therapy(67-69). This has led to the concept of 'delayed' or late LV reverse remodelling, though definitions vary between different authors(68, 69).

Banno et al (2016)(68) reported on a cohort of patients with HFrEF recruited between 2005 and 2011. 82.2% of patients were prescribed either an ACE inhibitor or ARB, with 91.5% prescribed a beta-blocker. The authors defined LV reverse remodelling as an increase in LV end systolic dimension (LVESD) of 15% or more combined with an increase in LVEF of 25% or more. 'Early' LV reverse remodelling was defined as occurring within 400 days post-enrolment and 'late' LV remodelling was defined as occurring between 400 and 1500 days post-enrolment(68). In this study, 31.8% of patients' left ventricles remodelled within 400 days post-enrolment with a further 7.8% of patients remodelling between 400 and 1500 days. Univariate analysis found only systolic blood pressure at baseline was associated with early LV reverse remodelling(68). Another cohort study, PROLONG (2017)(69), enrolled patients with a new diagnosis of HFrEF between 2012 and 2016. Patients were prescribed a combination of ACE inhibitors or ARBs (99% of patients), beta-blockers (96% of patients) and MRAs (89% of patients). In this study, LV reverse remodelling was considered 'delayed' if LVEF remained 35% or less after three months, but was subsequently greater than 35% after longer follow-up(69). Mean follow-up duration in this study was 12 months(69). After three months of medical treatment, 46.8% of patients had remodelled such that their LVEF was greater than 35%(69). After a further three months of medical treatment, a further 18.7% of

patients had an LVEF greater than 35%(69). No analysis of differences between patients who had early vs delayed LV reverse remodelling was reported.

Furthermore, several observational studies have reported LV reverse remodelling with either longer durations of medical therapy (up to 12 months) or in patients who switched to sacubitril/valsartan due to persistent HFrEF despite an ACE inhibitor or ARB. However, these studies do not explicitly refer to 'delayed' or 'late' remodelling (table 5).

Table 5 - LV reverse remodelling with longer medical therapy and/or change to sacubitril/valsartan

Study	**n**	**Treatment**	**Prior ACEi/ARB**	**LV reverse remodelling**
Januzzi 2019	794	Sacubitril-valsartan	75.8% of patients, duration not specified	LVEF % (median, IQR) Baseline 28.2 (24.5-32.7) 6 months 34.1 (29.0-39.7) 12 months 37.8 (32.3-45.2)
de Diego 2018	120	Sacubitril-valsartan	100% of patients, ≥9 months	LVEF % (mean, SD) Baseline 30.4 (4.0) 9 months 35.1 (8)
Martens 2019	151	Sacubitril-valsartan	100% of patients, median duration 4.3 years (1.4-8.4)	LVEF increased ≥5% in 44% of patients after mean 364 days
Guerra 2021	230	Sacubitril-valsartan	96.9% of patients, ≥6 months	LVEF increased to >35% in 25.2% of patients after 6 months

ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor II blocker, IQR – interquartile range, LVEF – left ventricular ejection fraction, SD – standard deviation

This concept of 'delayed' or late LV reverse remodelling (with or without a change in ACE inhibitor/ARB to ANRI) is important as it may affect ICD eligibility. Under current ESC guidelines(3), this means some patients receiving devices may no longer have an indication for the device following more prolonged OMT. If reassessment of LV function was delayed until patients have been on OMT for a longer duration, fewer patients may be eligible for a complex device. Individual patients would avoid the risk of both procedural and long-term device complications. It would also reduce healthcare costs. In this thesis, I will use the Duncker et al definition of delayed LV remodelling with LV reverse remodelling considered 'delayed' if LVEF remains 35% or less after three months, but is subsequently greater than 35% after longer follow-up(69) as this has the most relevance for ICD eligibility. Additionally, for simplicity the term 'delayed remodelling' will be used to refer to delayed LV reverse remodelling unless otherwise specified.

1.5.3 Safety of delaying device implantation

Due to delayed remodelling, it may be advantageous to delay device implantation until patients have been on OMT for longer than three months. However, consideration must be given to the safety of delaying device implantation, particularly ICDs and CRT-D given the risk of SCD in patients with HFrEF. In MADIT II, 19.7% of patients received appropriate therapy (ATP or shock to treat a ventricular arrhythmia) from their ICD over the course of the trial. However, the probability of receiving appropriate therapy increased over the duration of the study and the difference in mortality between the ICD and medical therapy groups did not become apparent until 12 months after the device implant. In SCD-HeFT, 21% of patients received a shock from their ICD over the course of five years of follow-up. However, the survival curves did not separate until after 12 months. Additionally, it should be noted that appropriate therapy does not necessarily equal a life saved. In a later analysis of the MADIT II data the absolute risk reduction (ARR) for mortality for patients in the ICD group compared to the medical therapy group was only 1% (confidence interval 4%) at 12 months, despite a shock rate of more than 15% over the same time period(70). The ARR for mortality at 12 months was similarly low in SCD-HeFT for patients in the ICD group compared to the medical therapy group, at 1% (confidence interval 4%) in the subgroup of patients with ischaemic heart disease (IHD) and 0% in the subgroup of patients with dilated cardiomyopathy (DCM) (70). Additionally, as already discussed, in the more recent DANISH

trial, whilst rates of SCD were lower in the ICD group compared to the control group, the difference in all-cause mortality was not statistically significant even over a mean follow-up duration of 67.6 months(38).

1.5.3.1 Declining SCD rates

Since MADIT II, SCD-HeFT and DANISH were published, some authors have suggested there has been a general trend towards lower rates of SCD in patients with HFrEF(58). Shen et al based their conclusions on lower rates of SCD in more recent clinical trials of patients with HFrEF(58) (table 6). In RALES (1999)(59) the rate of SCD per 100 patient years was 6.5%, in EMPHASIS-HF (2011)(71) it was 2.9% and in PARADIGM-HF (2014)(64) it was 3.3%(58). Furthermore, in the PROVE-HF study (2019)(72), which was published after Shen et al's review, the one year mortality was even lower at 0.8%(73). Each of the four classes of medication for HFrEF contribute to a reduction in the probability of SCD(59, 66, 74, 75). Particularly for ICDs, the trend towards reduced SCD is important to note, as this will likely reduce the additive benefit of these devices.

However, other authors have challenged the conclusions of Shen et al's review(76). Leyva et al argue that patients in different trials are not directly comparable, due to differing baseline characteristics(76). For example, in RALES (1999) 99.6% of patients had NYHA class III or IV symptoms(59). In EMPHASIS (2011), 0% of patients had NYHA class III or IV symptoms(71). However, this does not entirely explain the difference. PARADIGM-HF(2014) (64) and PROVE-HF (2019)(72) included similar proportions of patients with NYHA class III and IV symptoms (25.5% and 29.8% respectively), but SCD rates were far lower in the later study. Furthermore, whilst it may be argued that SCD rates in absolute terms are falling as medical therapy improves, the proportion of all deaths attributable to SCD does not appear to be changing (table 6). For example, in RALES (1999) the proportion of all deaths attributable to SCD was 28.9%, compared to 35.0% in EMPHASIS-HF (2011) and 33.7% in DAPA-HF (2019).

Table 6 - selected key heart failure trials, OMT and mortality rates

Trial	n (treatment group)	Follow-up duration	Background OMT	All cause mortality, n (%)	Sudden cardiac death, n (%)	SCD as % of all deaths
SOLVD 1991 - enalapril group	1285	48 months	8.3% beta-blockers	452 (35.2)	105 (8.2)	23.2
RALES 1999 - spironolactone group	822	24 months	95% ACEi 11% Beta-blockers	284 (35)	82 (10.0)	28.9
CIBIS 1999 - bisoprolol group	1327	1.3 years	96% ACEi	156 (12)	48 (4.0)	30.8
MADIT II 2002 - ICD group	742	20 months	68% ACEi 70% beta-blockers	105 (14.2)	28 (3.8)	26.7
SCD-HeFT 2005 - ICD group	829	45.5 months	94% ACEi/ARB 69% beta-blocker 19% MRA	182 (22.0)	37 (4.5)	20.3
EMPHASIS-HF 2011 - eplerenone group	1364	21 months	94% ACEi/ARB 87% beta-blocker 18% ICD/CRT-D	171 (12.5)	60 (4.4)	35.0
PARADIGM-HF 2014(77) - sacubitril/valsartan group	4187	27 months	93% beta-blocker 54% MRA 15% ICD	711 (17.0)	250 (6.0)	35.2
DANISH 2016 - ICD group	556	67.6 months	96% ACEi/ARB 92% beta-blocker 59% MRA	120 (21.6)	24 (4.3)	20.0
DAPA-HF 2019(66) - dapagliflozin group	2373	18.2 months	85% ACEi/ARB 11% ARNI 96% beta-blocker 72% MRA 26% ICD	276 (11.6)	93 (3.9)	33.7

ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor II blocker, CRT – cardiac resynchronisation therapy, ICD – implantable cardiovertor-defibrillator, MRA – mineralocorticoid receptor antagonist, OMT – optimal medical therapy, SCD – sudden cardiac death

1.6 Existing systematic reviews

As discussed in section 1.5.2, delayed remodelling could potentially reduce the number of patients eligible for complex devices, if decision-making regarding device implantation was delayed until patients had been on OMT for longer. However, delaying complex device implantation (particularly ICD) may increase the risk of SCD. Therefore, robust evidence is required if a change in guidelines is to be considered.

A search of systematic reviews highlighted a gap in the existing evidence. Existing reviews examining reverse remodelling either do not consider the concept of delayed remodelling (78, 79), only include RCT data,(78, 79) and/or are dated (80). Furthermore, earlier reviews have not addressed whether longer OMT affects device eligibility in patients with HFrEF(78-80). Lin et al examined the efficacy of sacubitril/valsartan in patients with HFrEF(79). However, the authors used an LVEF of 40% or less to define HFrEF, which, as described in section 1.4.2, is higher than the LVEF used by the ESC and NICE guidelines for ICD and CRT eligibility(12, 31, 79). Additionally, Lin et al's review included studies where patients' baseline OMT duration was either unclear(81), shorter than the three months for device eligibility(64), or there was no requirement for OMT at baseline(82). Bao et al explored the effects of different combinations of OMT on LV remodelling, but used a broader definition of HFrEF, including studies of patients with LVEF less than 50%(78). Wang et al explored the effect of sacubitril/valsartan and reported on change in LVEF at different time points(80). They reported improvements in mean LVEF after three months of sacubitril/valsartan, which increased further with longer treatment duration(80). However, Wang et al only included four studies of HFrEF reporting on the change in LVEF(80). Two of these studies were only published as abstracts(83, 84) and one included patients with a broader definition of HFrEF, including patients with an LVEF between 25% and 49% at baseline(85). Abstracts often contain insufficient information to assess eligibility and risk of bias and their inclusion in systematic reviews is controversial(86).

1.7 Objectives

Delayed remodelling could potentially reduce the number of patients eligible for complex devices. As discussed in section 1.4, there are potential negative impacts for individual

patients associated with receiving a complex device, and these devices are also costly. Therefore, it would be better for both individual patients and the wider health service if implantation could be safely avoided. However, there are potential risks in delaying complex device implantation, particularly for ICDs (and CRT-D). As discussed in section 1.4.1, ICDs reduce the risk of SCD in patients with HFrEF, and delaying ICD implantation may increase this risk.

As discussed in section 1.6, there is a gap in the existing evidence in this area. My objective was to undertake a systematic review of patients with HFrEF, who would be eligible for a primary prevention ICD under current NICE guidelines. This review aims to assess the rate of delayed LV remodelling such that patients would no longer considered eligible for an ICD. It also examines mortality rates in patients with HFrEF during longer duration medical therapy to assess the safety of any strategy to delay ICD implantation. As part of this review, CRT eligibility will also be considered given patients with an indication for a primary prevention ICD may also have an indication for CRT and these devices are frequently combined (CRT-D)(3, 12).

Chapter 2: Methods

The review protocol was designed in accordance with the Centre for Reviews and Dissemination (CRD) guidelines(87).

2.1 Eligibility

To ensure this review is clinically useful, it was necessary to limit the review to the patient groups commonly encountered in practice. The commonest aetiologies of heart failure are ischaemic heart disease, hypertension, dilated cardiomyopathy and valvular heart disease, which collectively comprise more than 90% of cases(7). Included studies were not limited to these four aetiologies. However, this was used as a starting point to exclude aetiologies, which may have skewed the review findings. For example, as this is a review of delayed remodelling, I excluded aetiologies of HFrEF that confer a significantly better or worse rate of remodelling compared to the commonest aetiologies. Additionally, to reduce confounders, non-drug interventions, which can influence remodelling were also excluded.

2.1.1 Higher rates of remodelling

Several aetiologies confer a higher than average rate of remodelling and were thus excluded. For example, complete recovery from LVSD in takotsubo cardiomyopathy occurs in more than 90% of patients within two months (88). For peripartum cardiomyopathy, LVEF is be expected to partially or completely recover in 87% of cases(89). In tachycardia-induced cardiomyopathy, normalisation of LVEF is expected for the majority of patients within six months of successful rhythm control(90). Similarly, reverse remodelling in acute coronary syndrome (ACS) is high, at 46% at six months in one study of patients following ST-elevation myocardial infarction(91).

Patients with chemotherapy-induced cardiomyopathy represent a challenging group. Many different chemotherapy agents are associated with heart failure, but uncertainties in treatment and prognosis remain(92). Prompt treatment produces high rates of remodelling for some types of chemotherapy-induced cardiomyopathy. One study reported remodelling rates of 82% within a mean of eight months of starting heart failure treatment in patients with anthracycline-induced cardiotoxicity(93). In this study, cardiotoxicity was identified

within a median of 3.5 months after anthracycline treatment, and standard heart failure medications started promptly. Data on duration of *optimal* medical treatment was not stated. For trastuzumab-induced cardiomyopathy, remodelling rates of between 87.5% and 97.3% have been described within 1.5 and 7.2 months of discontinuation of trastuzumab, with remodelling occurring in some patients without any specific heart failure treatment(94, 95). Therefore, I excluded patients with acute chemotherapy-induced cardiomyopathy. However, the definition of acute versus chronic is not clear and as such any cut-off is debatable. In Cardinale et al(93), the mean time to improvement was eight months after starting treatment, and treatment was started within a median of 3.5 months after anthracycline therapy. Therefore, I considered a baseline LVEF of 35% or less at least 12 months after the last dose of chemotherapy to be a reasonable cut-off for inclusion in this review.

2.1.2 Lower rates of remodelling

Several aetiologies are associated with progressive cardiomyopathy despite medical treatment and were also excluded. These aetiologies include Chagas cardiomyopathy(96) and primary valvular heart disease without surgical or percutaneous intervention(97). Aetiologies typically excluded from heart failure trials, such as the muscular dystrophies, were also excluded as the evidence-base for OMT is weaker(98).

2.1.3 Confounding interventions

Several non-drug interventions influence LV remodelling and were thus also excluded. Interventions for primary or secondary valvular heart disease, and ablation for atrial fibrillation or premature ventricular complexes are associated with LV remodelling(90, 99, 100).

Additionally, as discussed in section 1.4.2, CRT influences LV remodelling. Improvements have been shown by several trials after three to twelve months after CRT implant(50, 54, 61, 63). In CARE-HF(50) the largest change was seen within the first three months. In the other trials, reassessment of LV function was only performed after six or twelve months of CRT. A more recent observational study has reproduced these results and suggests that the

maximal effect of CRT is seen by 12 months for most patients(101). However, this study did not reassess the LV until at least six months after CRT implantation. As the greatest effect of CRT on remodelling is in the first three months, I used persistent LVEF of 35% or less three months post-CRT as an eligibility criterion. Studies in which patients were planned for CRT implantation during follow-up were excluded. However, given patients may be eligible for both a primary prevention ICD and a CRT, and such devices can be combined (CRT-D)(3, 12), CRT eligibility was recorded if reported in the included studies.

Although LV remodelling is common after ACS, data on the effects of coronary revascularisation is mixed. The REVIVED trial (2022) compared percutaneous coronary intervention plus OMT versus OMT alone in patients with HFrEF and severe coronary artery disease(102). It failed to demonstrate a difference in LV remodelling at six or twelve months(102). The earlier STITCH trial (2011) randomised HFrEF patients with coronary artery disease to surgical coronary revascularisation plus OMT or OMT alone(103). It demonstrated a statistically significant improvement in one measure of LV remodelling, LV systolic volume, by four months post-surgery(104). However, no difference in LVEF was seen. Different heart failure trials have adopted different approaches to patients with recent ACS or coronary revascularisation. Some trials have excluded patients with ACS and/or coronary revascularisation within the preceding one to six months(36, 50, 61, 81), whereas other trials did not excluded any patients on this basis(37, 73). Additionally, based on the data from DINAMIT(105) and IRIS(106), ICDs are not recommended within 40 days of an acute coronary syndrome. Given the conflicting research data and approaches any decision on including or excluding recent ACS or coronary revascularisation patients is a compromise. For simplicity, I used three months for both.

2.1.4 Participants

Studies were considered eligible for inclusion if they included participants that were aged 18 years or over and had a diagnosis of HFrEF using an LVEF of 35% or less to define severe LVSD. Additionally, participants must have had persistent LVEF of 35% or less despite at least three months of OMT.

Studies were excluded if they included participants that:

- had been taking OMT for 12 months or more at the time of the baseline LVEF assessment, unless they were newly starting staring sacubitril/valsartan
- had acute coronary syndrome (ACS) or coronary revascularisation less than three months prior to the baseline LVEF assessment
- had a CRT implanted less than three months prior to the start of the study or were planned to have a CRT implant during the baseline LVEF assessment
- had surgical or percutaneous intervention for valvular heart disease less than three months prior to the baseline LVEF assessment
- had untreated severe primary valvular heart disease
- had an ablation procedure for atrial fibrillation or premature ventricular complexes less than three months prior to the baseline LVEF assessment
- had a reversible cause of HFrEF, including tachycardia-induced cardiomyopathy, takotsubo cardiomyopathy or peripartum cardiomyopathy
- had an aetiology of HFrEF typically progresses despite treatment, such as chagas cardiomyopathy
- had HFrEF secondary to chemotherapy unless the last dose of chemotherapy was given more than 12 months prior to the baseline LVEF assessment
- had complex congenital heart disease

Studies that included subgroups that met the eligibility criteria were included provided the target subgroup data was reported separately. In practice, LVEF may be assessed using echocardiography, cardiac MRI and nuclear imaging. However, nuclear techniques are rarely used(3). Additionally, correlation between methods is poor(107). Therefore, I only included studies where the same imaging technique had been used for both the baseline and follow-up assessment of LVEF.

2.1.5 Intervention

The intervention of interest is prolonged (more than three months) OMT for HFrEF. Current OMT is a combination of four classes of drugs(3) (see section 1.2). However, it should be noted that OMT is patient specific. Whilst the aim is to achieve maximum doses of each of the four classes of medications, individual patients differ in their tolerance both to individual

drugs and their doses. Therefore, no specific combination of medications or doses were specified for inclusion. However, there are two caveats to this. Firstly, patients had to have been on OMT for at least three months as judged by the study investigators. Secondly, OMT needed to reflect current practice. As discussed in section 1.2, OMT has developed over many years with the publication of key trials demonstrating superiority of new medications over existing therapy. One example is sacubitril/valsartan (an ARNI), which was licensed in 2015 after the publication of the PARADIGM-HF trial a year earlier(64). It has since become the standard of care for patients with persistent HFrEF despite treatment with ACE inhibitors/ARB, being incorporated into NICE and ESC guidelines in 2016(55, 108). Therefore, I only included trials where sacubitril/valsartan was a treatment option. However, not all patients tolerate sacubitril/valsartan(109, 110). For such patients, continued ACE inhibitor/ARB represent OMT. Therefore, trials of patients not on sacubitril/valsartan were included provided patients were not taking it due to intolerance, rather than lack of availability.

Current OMT includes the use of an SGLT2 inhibitor (if tolerated). However, this class was only licensed for heart failure in 2020, after the publication of the DAPA-HF trial in 2019(65). I anticipated that few studies would include patients treated with SGLT2 inhibitors. However, a recent systematic review found no impact of SGLT2 inhibitors on LVEF(111). Therefore, the use of SGLT2 inhibitors did not form part of the inclusion criteria for the review. However, a pre-specified subgroup analysis for studies of patients taking SGLT2 inhibitors was considered, depending on the studies included.

2.1.6 Outcomes

The primary and secondary outcomes of interest were those occurring after a minimum of an additional three months of OMT. Outcomes reported at longer additional durations of OMT (e.g., six, nine, twelve months etc) were also recorded. Outcomes were reported either with reference to the patients baseline duration of OMT (between three and 12 months) or with reference to a change in ACE inhibitor/ARB to ARNI.

Primary outcomes:

1. Proportion of patients that positively remodel such that their LVEF is greater than

35%

2. Proportion of patients with significant positive remodelling (improvement in LVEF of 5% or more)

A 5% change in LVEF has been used in several heart failure studies to represent a significant change(112, 113). Additionally, as discussed every 5% reduction in LVEF below 45% increases the composite of death and heart failure hospitalisation by 13%(13). Therefore, I consider an increase in LVEF of more than 5% clinically significant.

Secondary outcomes:

1. Mean/median change in LVEF
2. Mortality
3. Heart failure hospitalisation
4. Implantable Cardioverter-Defibrillator (ICD) therapy - anti-tachycardia pacing (ATP), shocks (both appropriate and inappropriate)
5. Change in New York Heart Association (NYHA) class
6. Heart failure medications - proportion of patients (and percentage of maximum dose) on each of ACE inhibitor, ARB, ARNI at baseline and end of follow-up

The secondary outcomes of mortality and heart failure hospitalisation assess whether there is an increased risk of adverse outcomes associated with delayed device implantation. Whilst mortality is of greater interest given the review's focus on primary prevention ICDs, heart failure hospitalisation is also important. CRT eligibility was considered as part of the review and CRT reduces heart failure hospitalisation(50-52, 63).

2.1.7 Types of study

Randomised-control trials, cohort studies and case-control studies were included.
There were no restrictions based on clinical context; studies in inpatient, outpatient, home or institutional settings were included. Reviews, case reports, case series, abstracts and conference proceedings were excluded. Information in abstracts and conference proceedings is often inadequate to assess eligibility and risk of bias(86).

2.2 Search strategy

The following electronic databases were searched: MEDLINE (Ovid), EMBASE (Ovid), CINAHL Ultimate (EBSCO), Cochrane Trials and Cochrane Database of systematic reviews, and Web of Science, restricted to dates between 01/01/2014 to 20/04/2023. This date restriction was chosen as the pivotal ARNI trial, PARADIGM-HF, was published in 2014(64). As discussed in section 2.1.5, ARNI are the current standard of care for patients with persistent HFrEF despite ACE inhibitor/ARB.

Relevant reviews identified during screening were tagged and their reference list checked for relevant studies which had been missed.

The search strategy was devised in collaboration with a specialist librarian at Hull York Medical School. The search strategy can be found in appendix 1.

2.2.1 Language

Only studies published in English were included in the final analysis due to time and financial constraints. However, relevant studies not published in English were included in the search and exclusions based on language were recorded. A recent systematic review of method studies found that there was a minimal impact on effect size and conclusions of systematic reviews through restricting searches to studies published in English(114).

2.2.2 Study selection

Covidence (www.covidence.org) is a web-based application created for use in systematic reviews, which is designed to assist in ensuring integrity in the review process(115). Covidence was used for both screening and data extraction. Identified studies were imported into Covidence, which automatically excluded duplicate studies. In the first screening stage, the titles and abstracts for all studies were reviewed independently by two reviewers (LW and VJ) for inclusion or exclusion. Disagreements were resolved by consensus, or where consensus could not be reached, resolved in consultation with a third reviewer (CW). In the second screening stage, the full texts of all included studies were obtained and similarly independently reviewed by two reviewers (LW and VJ) for inclusion or exclusion in the final review. A similar mechanism was utilised for resolving conflicts.

Reasons for exclusion were recorded for the full text stage. I contacted authors for clarification if a published report was unclear on one eligibility criterion, provided the other criteria were met. The exception to this was baseline LVEF for studies with a stated inclusion criterion of LVEF 40% or less. Obtaining clarification from authors for these studies was likely to require sharing of patient-level data, which I deemed not to be feasible within the timeframe available for completing the review.

2.3 Data extraction

Data was extracted by one reviewer (LW) and a random sample of 10% of studies was checked by a second reviewer (VJ). Disagreement was resolved by consensus or, if consensus was not reached, by consultation with a third reviewer (CW).

An a priori data extraction form was created in Covidence and piloted with two studies. A summary of data that was extracted for each study is shown in table 7.

Table 7: Data extracted for each included study

General information	Title First author's name Publication year Study location (country)
Study characteristics	Study type Start and end dates Funding sources Possible conflicts of interest for study authors
Participant information	Inclusion and exclusion criteria Recruitment method Sample size
Baseline participant data	Age Gender Proportion with ischaemic heart disease Systolic blood pressure and heart rate AF history Creatinine and estimated glomerular filtration rate NYHA class LVEF, LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) Proportion with moderate or severe mitral regurgitation Proportion on each heart failure medications (for ACE inhibitor, ARB, ARNI, MRA, BB and SGLT2 inhibitor) Percentage maximum dose of ACE inhibitor, ARB and ARNI Proportion with an ICD or CRT and time

	since implant CRT eligibility
Outcome data	Duration of OMT Number with LVEF greater than 35% Number with significant positive remodelling Mean change in LVEF, LVEDV and LVESV Mortality Heart failure hospitalisation Change in NYHA class Number of ICD or CRT implants during follow-up ICD therapy and complications Medications and percentage maximum dose (for ACE inhibitor, ARB and ARNI)

ACE - angiotensin converting enzyme, AF - atrial fibrillation, ARB - angiotensin receptor blocker, ARNI - angiotensin receptor blocker/neprilysin inhibitor, BB - beta-blocker, CRT - cardiac resynchronisation therapy, ICD - implantable cardioverter-defibrillator, LVEDV - left ventricular end-diastolic volume, LVEF - left ventricular ejection fraction, LVESV - left ventricular end-systolic volume, MRA - mineralocorticoid receptor antagonist, NYHA - New York Heart Association, SGLT2 - sodium-glucose co-transporter 2

2.4 Assessment of bias

The Newcastle-Ottawa scale (NOS) was used for non-randomised studies to assess for risk of bias for each full text included after stage 2 review(116). Assessments were performed by a single reviewer (LW) and checked by a second reviewer (VJ). Disagreement was resolved by consensus or, if consensus was not reached, by consultation with a third reviewer (CW). Each NOS domain contains two to four possible criteria (a to d), which can be converted into a numerical score for each domain with higher scores indicating a lower risk of bias(116). These numerical scores can then be added to give a summary score for each study(116). However, the validity of summary scores is questionable(87). Jüni et al found no relationship

between summary scores and treatment effects in their 1999 meta-analysis(117). Other authors have criticised summary scores for giving weight to domains that may not be relevant to the validity of the study outcomes(118, 119). Additionally, the conversion of individual domains into numerical scores would hide heterogeneity between studies(118). For example, in the assessment of outcome domain, NOS gives the same score to 'independent blind assessment' and 'record linkage'(116). These two methods could produce different risks of bias(118). Therefore, the risk of bias assessment was reported separately for each domain. Finally, the risk of bias as a result of measurement error was considered in greater detail than the NOS proforma allows. There is both intra- and inter-observer variability in TTE assessments of LVEF(120, 121) and it was anticipated that TTE would be the predominant imaging modality used in studies to assess LVEF. Variability in LVEF measurement are particularly relevant if changes in LVEF at different timepoints are small and if small changes in LVEF change eligibility for complex implantable devices. Therefore, intra- and inter-observer variability in the reported studies was considered as part of the risk of bias assessment.

Studies were included in the synthesis regardless of risk of bias, but this was reported for each study to inform my confidence in the results, which was reflected in the conclusions and implications for practice sections of the review.

2.5 Data synthesis

As stated in the Centre for Reviews and Dissemination guidance for undertaking systematic reviews in healthcare, data synthesis involves the collation and summation of the findings of individual studies(87). Due to the heterogeneity between the populations and methodologies in the included studies, combining the results in a meta-analysis would not be recommended(87). As such, a meta-analysis was not performed. Therefore, this review utilises a narrative synthesis. The structure of the synthesis is based on the framework established by the Economic and Social Research Council (ESRC)(122), which comprises a four-stage approach:

- Developing a theory of how the intervention works, why and for whom
- Developing a preliminary synthesis of findings of included studies

- Exploring relationships in the data
- Assessing the robustness of the synthesis

I started with a descriptive summary of the studies, including characteristics, key findings and risk of bias. Data was then synthesised according to the main and additional outcomes. For the main outcomes, the proportions of participants with significant remodelling and remodelling to LVEF greater than 35% were reported alongside absolute numbers and the sample size of the study. Several pre-specified moderator variables were considered for data synthesis. This included variables both at a study level (quality, design, setting), and for sample characteristics. In particular, sample characteristic variables known to affect either mortality or LV remodelling rates in HFrEF were considered (see section 1.3), including age, baseline LVEF, NYHA class, AF, mitral regurgitation, ischaemic heart disease, renal dysfunction, NT-proBNP levels and OMT doses. Three patient characteristics were pre-specified for subgroup analysis. These included baseline medical therapy (ACE inhibitor/ARB versus ARNI), presence of absence of CRT, and aetiology of heart failure (ischaemic versus non-ischaemic). Finally, there is a critical discussion of methodology and evidence used (quality, validity, generalisability) with an emphasis on possible sources of bias.

Chapter 3: Results

3.1 Study selection

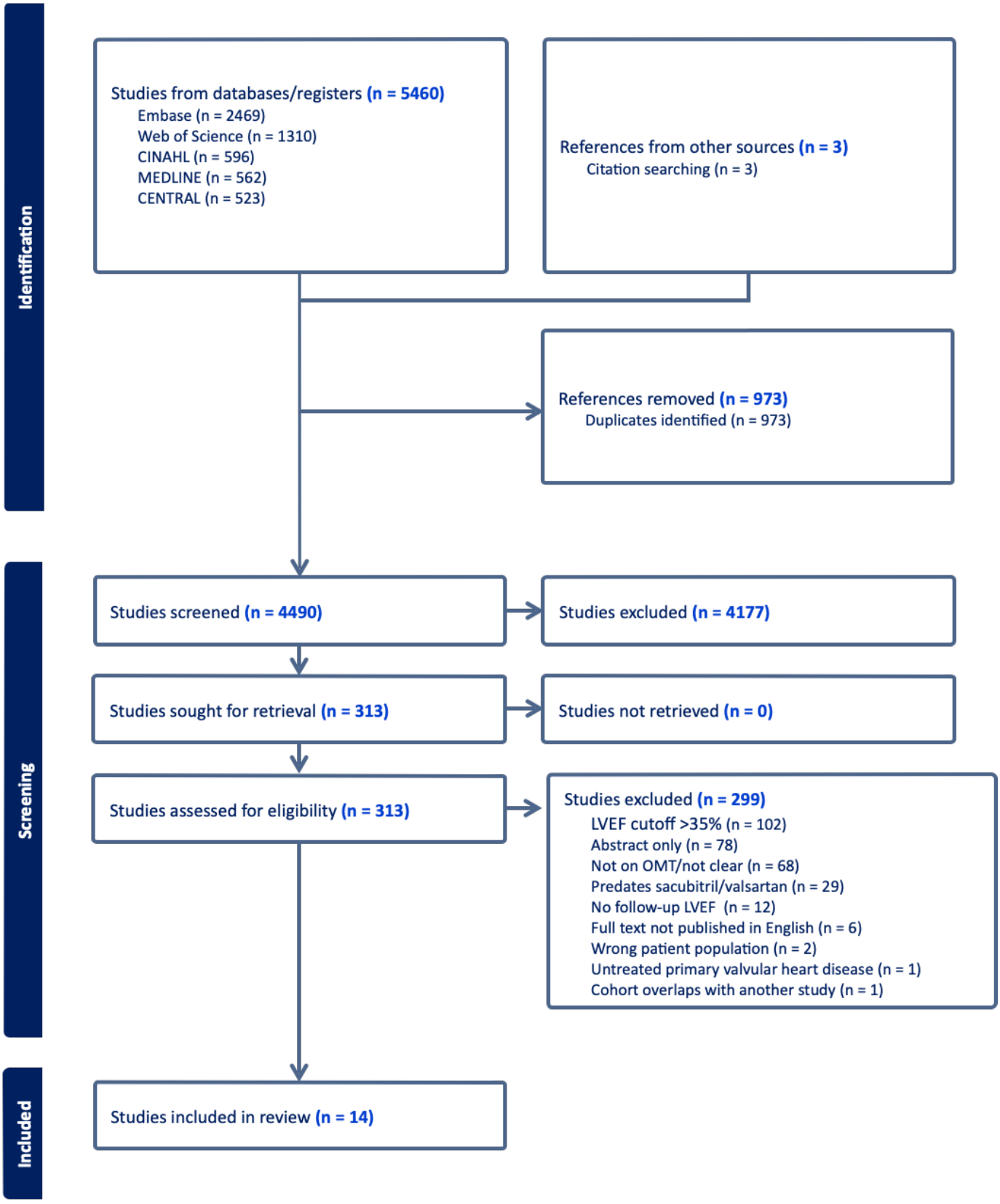
3.1.1 Electronic databases search

A total of 5460 studies were identified. The results were imported into Covidence, where 973 duplicates were excluded. Therefore, 4490 studies were included for title and abstract screening (figure 3).

Hand searching of the relevant systematic reviews identified during the initial screening identified three further potentially eligible studies. These studies were imported into Covidence and went through the same screening process as all other studies.

Title and abstract screening excluded 4177 studies, leaving 313 studies for full-text review (figure 3).

Figure 3: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram



3.1.2 Excluded studies

The commonest reason for exclusion after full-text review was studies using an LVEF cut-off of greater than 35% and not reporting results for the subgroup of their cohort with an LVEF of 35% or less (n=104) (figure 3). Many studies used an LVEF of 40% or less as an inclusion criterion. As discussed in section 1.1, this is due to different definitions of HFrEF being used in different clinical guidelines(3, 8, 9).

Sixty-eight studies were excluded due to patients either not being on OMT (or unclear) or not being on OMT for a sufficient length of time. However, for five studies baseline OMT was unclear, but the studies met all the other eligibility criteria, *and* one or more comments were present in the published report suggesting that the study may meet the OMT criteria. For example, one study reported that patients were in “a clinically stable condition for at least three months", but no comment was made about duration of OMT at baseline(123). In another study, patients had to be prescribed an optimal dose of either an ACE inhibitor or an ARB for at least four weeks to be included in the study(124). However, elsewhere in the report, the authors reported that the median duration of heart failure before initiation of sacubitril/valsartan was 3.3 years(124). Given this duration of heart failure, I would expect patients to have been on OMT for more than three months. However, as this was not clear from the report, the authors were contacted. In total, authors for five studies were contacted to seek clarification about baseline OMT where this was unclear from the published report and was the only potential reason for excluding the study from the review. Two authors responded, confirming that their respective studies both met the review eligibility criteria. The remaining three authors did not respond, and their studies were excluded (table 8).

Overlap between cohorts in different publications was suspected in eight studies, which were initially included after full-text review (table 9). All these studies were conducted in Italy. The authors for each of these studies were contacted. Authors for one set of overlapping studies responded, confirming significant overlap between cohorts and advising that the earlier publication be excluded (table 8). Thus, a total of 299 studies were excluded after full-text review.

Table 8: Studies excluded after contacting authors

Study	Response from authors	Reason for excluding
Martens 2018(124)	No	Baseline OMT duration unclear
Mantegazza 2021(123)	No	Baseline OMT duration unclear
Viliani 2020(125)	No	Baseline OMT duration unclear
Casale 2021(126)	Yes	Cohort overlaps with later/larger publication

OMT - optimal medical therapy

Table 9: Overlap/suspected overlap between study cohorts

Study	Location	Recruitment dates	n
Foggia studies			
Correale 2020(127)	- University Policlinic Hospital of Foggia	September 2016 - January 2019	60
Gioia 2022(128)	- University Policlinic Hospital of Bari - University Policlinic Hospital of Foggia	2016 - 2019 2019 - 2021	80
Messina studies			
Casale 2021(126)	• - AOU Policlinico G Martino, Messina	December 2017 - October 2018	41
Corrado 2022(129)	- University of Messina - University Hospital of Palermo	October 2017 - June 2019	90
Palermo Studies			
Corrado 2022(129)	- University of	October 2017 - June	90

	Messina - University Hospital of Palermo	2019	
Giallauria 2020(130)	- Buccheri La Ferla Fatebenefratelli Hospital - Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo	Not stated	134
Romano 2019(131)	- Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo	September 2017 - January 2019	216
Vitale 2019(132)	- Buccheri La Ferla Fatebenefratelli Hospital - Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo	Not stated	125

3.2 Study characteristics

Fourteen studies were included in the final review. Further details of the individual studies are shown in table 10. One reviewer (LW) performed the data extraction and a random sample of two studies was checked by a second reviewer (VJ).

Table 10: List of included studies

Study	Location	Sample size	Design	Objectives
Cemin 2023(133)	Italy	79	Prospective cohort	Confirm the effect of sacubitril/valsartan on NYHA class, NT-proBNP, furosemide dose, LV remodelling, HF hospitalisation and mortality in HFrEF patients
Corrado 2022(129)	Italy	96	Prospective cohort	Evaluate clinical and functional effects in low- vs high-dose sacubitril/valsartan in HFrEF patients
Correale 2020(127)	Italy	60	Cohort[#]	Evaluate the effect of sacubitril/valsartan on RV function in patients with HFrEF
Frey 2021(134)	Austria	21	Retrospective cohort	Assess tolerability of sacubitril/valsartan in patients with a history of cancer in a real-world setting
Giallauria 2020(130)	Italy	134	Prospective cohort	Evaluate the effects of sacubitril/valsartan on autonomic function in patients with HFrEF
Gioia 2022(128)	Italy	80	Cohort[#]	Clarify the effects of sacubitril/valsartan on renal resistance index
Guerra 2021(113)	Italy	230	Prospective cohort	Evaluate how many patients with HFrEF and primary prevention ICD did not meet the indication criteria for ICD implant after 6 months of treatment with sacubitril/valsartan
Malfatto 2019(135)	Italy	35	Retrospective cohort	Describe the effects of sacubitril/valsartan on CPET in patients with HFrEF
Martens 2019(112)	Belgium	151	Retrospective cohort	Evaluate the effect of sacubitril/valsartan on ventricular arrhythmia prevalence in patients with HFrEF

Monzo 2021(136)	Italy	55	Retrospective cohort	Assess the impact of sacubitril/valsartan on ICD eligibility in patients with HFrEF
Paolini 2021(137)	Italy	69	Prospective cohort	Evaluate the effect of sacubitril/valsartan on LV remodelling in patients with HFrEF
Romano 2019(131)	Italy	216	Prospective cohort	Assess the effects of sacubitril/valsartan on clinical, biochemical and echocardiographic, parameters in HFrEF patients
Russo 2022(138)	Italy	190	Prospective cohort	Evaluate the clinical impact of sacubitril/valsartan among CRT-D non-responder patients
Vitale 2019(132)	Italy	125	Prospective cohort	Evaluate the effects of sacubitril/valsartan on CPET parameters in HFrEF patients

#Unclear if prospective or retrospective

CPET - cardiopulmonary exercise test, CRT-D - cardiac resynchronisation therapy/defibrillator, HFrEF - heart failure with reduced ejection fraction, ICD - implantable cardioverter-defibrillator, LV - left ventricular, NT-proBNP - N-terminal pro B-type natriuretic peptide, NYHA - New York Heart Association, RV - right ventricular

3.2.1 Study design

All 14 studies were single cohort observational studies, which examined the effect of sacubitril/valsartan in patients with HFrEF who had persistent LVEF of 35% or less despite treatment with OMT, which included optimal doses of either an ACE inhibitor or ARB. Eight studies were prospective(113, 129-133, 137, 138) and four studies(112, 134-136) were retrospective. It was not clear whether the remaining two studies were prospective or retrospective(127, 128). Twelve studies were conducted in Italy(113, 127-133, 135-138), and one each in Austria(134) and Belgium(112).

3.2.2 Population characteristics

A total of 1541 patients were included across the 14 studies (mean 109, range 21-230). However, 85 patients either withdrew from the studies or were lost to follow-up, resulting in 1456 patients included in the final analysis. The mean age of included patients was 63.4 years and 77.3% of patients were male (range 51%-88%). Only one study had a similar number of male and female patients (51% male)(134).

As discussed in section 1.3, several factors are associated with a poor prognosis in HFrEF. This includes LVEF, which was similar across all studies. Baseline LVEF ranged from 26.8% to 34.0%. As stated, an LVEF of 35% or less at baseline was an inclusion criterion in all studies.

3.2.2.1 New York Heart Association (NYHA) class

The included studies were broadly similar in terms of baseline NYHA class. Ten studies reported a breakdown of baseline NYHA class I to IV (table 11)(112, 113, 128-133, 136, 137). Two studies only reported mean NYHA class, which was 2.9+/-0.4(134) and 2.2+/-0.4(135). The final study reported median NYHA class II (range 2-3)(138). All studies had a majority of patients with NYHA class II symptoms at baseline and fewer than 5% of included patients were NYHA class I or IV.

Table 11: Baseline New York Heart Association (NYHA) class

Study	**NYHA class (%)**			
	I	II	III	IV
Cemin 2023(133)	0	33	67	0
Corrado 2022(129)	0	63	37	0
Correale 2020(127)	0	71	29	0
Giallauria 2020(130)	4	62	35	0
Gioia 2022(128)	0	74	26	0
Guerra 2021(113)	1	55	43	1
Martens 2019(112)	0	68	30	2
Monzo 2021(136)	0	56	52	2
Paolini 2021(137)	0	52	48	0
Romano 2019(131)	0	62	38	0
Vitale 2019(132)	0	63	37	0

NYHA - New York Heart Association

3.2.2.2 Systolic blood pressure

Baseline systolic blood pressure was reported in 11 studies(112, 127-134, 136, 137). The mean baseline systolic blood pressure varied between 115 and 131mmHg.

3.3.2.3 Renal function

Nine studies reported baseline estimated glomerular filtration rate (eGFR)(113, 128,

130-133, 135-137). The mean baseline eGFR in these studies was 67.7ml/min/1.73m2. One study reported creatinine, but not eGFR(112). In this study, the mean baseline creatinine was 1.27+/-0.39mg/dl(112). One study excluded patients with an eGFR less than 60ml/min/1.73m^2(129). Two studies excluded patients with an eGFR less than 30ml/min/1.73m^2(127, 134).

3.2.2.4 Mitral regurgitation (MR)

Only five studies reported on the prevalence of moderate or severe mitral regurgitation in their population(113, 131, 136-138). This varied significantly between studies, ranging from 30% to 85% (table 12).

3.2.2.5 Atrial fibrillation (AF)

Studies also differed in the prevalence of AF in their populations. One study specifically excluded patients with a history of AF(129). Two studies did not report the prevalence of AF in their population(127, 135). In the remaining 11 studies, the median prevalence of AF was 33%, but with a wide range (8% to 47%) (table 12)(112, 113, 128, 130-134, 136-138).

3.2.2.6 NT-proBNP

Baseline NT-proBNP levels differed between the ten studies which reported them, ranging from 1027 to 3873pmol/l (table 12)(127-136). The average level of serum NT-proBNP also differed within studies with large standard deviations (SD) or ranges reported in most studies (table 12). This suggests a degree of heterogeneity within each of these studies' populations.

3.2.2.7 Ischaemic heart disease (IHD)

The prevalence of ischaemic heart disease was reported in 13 studies(112, 113, 127-129, 131-138). This varied greatly between studies, ranging from 33% to 72% (table 12).

Table 12: Baseline prevalence of moderate or severe MR, AF, IHD and baseline mean NT-proBNP

Study	Moderate or severe MR (%)	AF (%)	IHD (%)	Mean/median NT-proBNP (pmol/l) (SD or IQR)
Cemin 2023(133)	Not reported	18	53	3265 (1548-5493)
Corrado 2022(129)	Not reported	0	72	1650 (1301)
Correale 2020(127)	Not reported	Not reported	43	3049 (5775)
Frey 2021(134)	Not reported	43	33	3873 (3140)
Giallauria 2020(130)	Not reported	16	Not reported	1443 (1323)
Gioia 2022(128)	Not reported	8	36	1052 (1321)
Guerra 2021(113)	71	33	47	Not reported
Malfatto 2019(135)	Not reported	Not reported	66	1195 (1039)
Martens 2019(112)	Not reported	41	69	Not reported
Monzo 2021(136)	31	40	63	1027 (879-1560)
Paolini 2021(137)	31	40	33	Not reported
Romano 2019(131)	30	17	46	1865 (2318)
Russo 2022(138)	85	47	42	Not reported
Vitale	Not reported	17	51	1200 (446-

2019(132)				2120)

AF - atrial fibrillation, IHD - ischaemic heart disease, IQR - interquartile range, MR - mitral regurgitation, NT-proBNP - N-terminal pro B-type natriuretic peptide, SD - standard deviation

3.2.2.8 Optimal medical therapy (OMT)

All 14 studies reported baseline ACE inhibitor and ARB use prior to switching to sacubitril/valsartan. Ten studies reported that all patients were prescribed an ACE inhibitor or ARB at baseline(112, 113, 127-129, 131, 134-136, 138). For the remaining four studies, ACE inhibitor/ARB prescriptions at baseline varied between 81% and 95% of the population(130, 132, 133, 137). Three of these studies only included patients that had been prescribed an ACE inhibitor or ARB at the maximum tolerated dose for six months(130, 132, 133). The final study reported that all patients were prescribed OMT at baseline(137). Only two studies reported percentage of maximum dose ACE inhibitor or ARB(112, 128). In Gioia et al(128), 68% of patients were prescribed more than 50% of the maximum dose of ACE inhibitor or ARB. Martens et al(112) reported that the mean dose of ACE inhibitor or ARB at baseline was 58% (+/- 30%).

All studies reported baseline beta-blocker prescriptions, which varied between 86% and 100% of patients. Additionally, all studies reported baseline MRA prescriptions, which varied from 54% to 91% of patients. No studies included patients treated with SGLT2 inhibitors at baseline. SGLT2 inhibitors did not enter ESC guidelines until 2021(3), which was after most studies had completed recruitment.

3.2.2.9 Complex implantable devices

CRT eligibility at baseline was not reported by any of the included studies, and only one study reported the proportion of patients with a CRT at both baseline and follow-up(130). In this study, 17% of patients had a CRT at baseline, which increased to 18% after 12 months(130). Eleven studies included variable proportions of patients with CRT at baseline, ranging from 12% to 100%(112, 128-135, 137, 138). This may suggest that many patients were not eligible for CRT, although there is some evidence that CRT is currently underutilised in eligible patients with HFrEF(139). Two of these studies did not specify a

minimum duration after CRT implantation for inclusion(128, 134). Eight of these studies specified a minimum time post-CRT for inclusion, ranging from three to twelve months(112, 129-133, 135, 138). One study only included patients who were CRT non-responders, which the authors defined as an improvement in LVESV of less than 15% despite at least 12 months of CRT(138). Another study only included patients with a CRT if they were CRT 'non-responders', though did not report a specific timescale or criteria to assess non-response(137). One study included patients with CRT-D, though did not report the prevalence of ICD and CRT-D separately(127). Two studies excluded patients with CRT at baseline (113, 136).

All 14 studies included a variable number of patients with an ICD (or CRT-D) at baseline. The prevalence varied from 29% to 100% of patients.

3.2.3 Risk of bias

As discussed in section 2.4, risk of bias assessment was performed using the Newcastle-Ottawa scale (NOS)(116). Modifications to the NOS were required as all of the included studies only comprised a single cohort of patients. Therefore, the domains on selection of the non-exposed cohort and comparability between cohorts were not relevant. This impacted the maximum attainable summary score. However, as discussed in section 2.4, the validity of summary scores is questionable(87) and thus I had already decided not to calculate any. I have reported each individual domain using the NOS letter gradings (table 13).

Table 13: Summary of Newcastle-Ottawa Scale by study and domain (NOS proforma reproduced in appendix 3)

Study	**Selection**			**Outcome**		
	Representativeness of the cohort	**Ascertainment of exposure**	**Demonstration that outcome of interest not present at start of study**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up**
Cemin 2023(133)	b	a	a	a	a	b
Corrado 2022(129)	b	a	a	a	a	b
Correale 2020(127)	b	a	a	a	a	d
Frey 2021(134)	c	a	a	b	a	b
Giallauria 2020(130)	b	a	a	a	a	d
Gioia 2022(128)	b	a	a	b	a	b
Guerra 2021(113)	b	a	a	b	a	b
Malfatto 2019(135)	b	a	a	b	a	c

Martens 2019(112)	b	a	a	b	a	a
Monzo 2021(136)	b	a	a	a	a	b
Paolini 2021(137)	b	a	a	a	a	c
Romano 2019(131)	b	a	a	a	a	a
Russo 2022(138)	b	a	a	a	a	a
Vitale 2019(132)	b	a	a	b	a	a

Each domain is graded in one of two to four categories (lettered a to d), with 'a' representing the lowest and 'd' the highest risk of bias(116). *Low risk of bias grades (as per NOS criteria) are highlighted in yellow. See appendix 3 for reproduction of NOS proforma*

3.2.3.1 Representativeness of the cohort

Selection bias can occur when the study sample is not representative of the population(140). This can be by not including eligible patients in the study to begin with(140). Apart from Frey et al who only included patients with HFrEF if they had a prior history of cancer(134), there is nothing in the reported *methodology* of the other 13 included studies that suggests systematic underrepresentation of one group or another. However, the reported results suggest under-representation of older patients and patients with co-morbidities when the included studies are compared to registry data of patients with HFrEF(141).

3.2.3.2 Assessment of outcomes

Blinding

Bias may be introduced if outcomes are measured by assessors who are aware of the intervention(140). Studies differed in their method of assessing outcomes (table 13). In seven studies, the clinician performing the follow-up assessment of LV function was blinded to the patient's study participation(129-131, 133, 136-138). In the remaining six studies, the follow-up assessment was obtained either retrospectively from clinical records or no statement was made about blinding(112, 113, 128, 132, 134, 135), which could bias the results.

Measurement error

All 14 studies used TTE to assess LVEF(112, 113, 127-138). Three of the included studies reported intra- and/or inter-observer variability for their echo measurements (table 14)(113, 129, 133).

Table 14: Intra- and inter-observer variability in LVEF

Study	Mean LVEF improvement	Intra-observer variability for LVEF	Inter-observer variability for LVEF
Cemin 2023(133)	3%		3.7%+/-3%
Corrado 2022(129)	4%		5.2% (95% CI 3.4%–6.3%)
Guerra 2021(113)	3.9%	2.6%	3.4%

CI - confidence intervals, LVEF - left ventricular ejection fraction

Whilst the inter-observer variability in the three studies that reported this outcome was small (table 14), it is sufficiently large to impact on the confidence in the results, particularly given the small changes in mean LVEF reported in most of the included studies. Indeed, the inter-observer variability reported by Corrado et al was 5.2%(129), which is higher than the mean change in LVEF reported in all but three of the included studies (table 18, section 3.4.1). The impact of intra- and inter-observer variability for LVEF measurements may be higher for the six studies where LVEF assessments were not clearly blinded(112, 113, 128, 132, 134, 135).

3.2.3.3 Adequacy of follow-up

Adequacy of follow-up differed between the studies (table 15). Only two studies included all patients in the final analysis regardless of loss to follow-up(133, 134). Missing data may introduce attrition bias depending on the reason why it is missing(142). Two studies reported no loss to follow-up(112, 138), though in one of these studies data was collected retrospectively(112). However, in this retrospective study, whilst loss to follow-up was 0%, only 73% of patients had a follow-up assessment of their LV function(112). Seven studies reported loss to follow-up of less than 20% of the sample size(113, 128, 129, 131, 133, 134, 136). Three studies reported loss to follow-up of more than 20% of the sample size(132, 135, 137). In Malfatto et al(135), no patients were lost to follow-up after six months, but this rose to 37% after 12 months of follow-up. Two studies made no statement on loss to follow-up(127, 130). Higher rates of attrition affect the confidence in the effect size(143).

Consideration must also be given to studies reporting low rates of drug discontinuation.

Lower than expected drug intolerance in the included studies limits the applicability of the study findings to a wider heart failure population, where far more patients may not tolerate sacubitril/valsartan for long enough to see an improvement in their LVEF. Six studies reported reasons for loss to follow-up, which was predominantly secondary to intolerance to sacubitril/valsartan(128, 129, 133, 134, 136, 137). For example, Russo et al reported 2.3% of patients stopped sacubitril/valsartan due to drug intolerance over the course of 12 months(138). In Paolini et al, this rate was 5.8% over the course of 24 months(137). Far higher rates of discontinuation have been reported in other studies of sacubitril/valsartan in patients with HFrEF. In PARADIGM-HF, over a median follow-up duration of 27 months, 17.8% of patients discontinued sacubitril/valsartan(64). Additionally, in this same trial, 5.8% of patients discontinued sacubitril/valsartan during the run-in phase (median duration 29 days IQR 26-35)(64). In registry data of heart failure patients, discontinuation rates of sacubitril/valsartan vary from 14.7% to 40.3% at one-year post-initiation(144). This potentially means that the results of this review are not applicable to a proportion of the wider HFrEF population, where a smaller overall effect size may be expected due to higher rates of drug discontinuation.

Table 15: Attrition rate

Study	Sample size	Attrition
Malfatto 2019(135)	35	0% at 6 months 37% at 12 months
Martens 2019(112)	151	0% for ICD outcomes 27% for LVEF outcomes
Paolini 2021(137)	69	25%
Vitale 2019(132)	125	21%
Frey 2021(134)	21	19%
Gioia 2022(128)	80	18%
Monzo 2021(136)	48	15%
Cemin 2023(133)	79	14%
Corrado 2022(129)	96	6%
Romano 2019(131)	216	5%
Guerra 2021(113)	230	2%
Russo 2022(138)	190	0%
Correale 2020(127)	60	No statement
Giallauria 2020(130)	134	No statement

ICD - implantable cardioverter-defibrillator, LVEF - left ventricular ejection fraction

3.2.3.4 Reporting bias

Selective reporting is not unique to observational studies and is often driven by a desire to only publish findings that are sufficiently noteworthy(140). This desire could result in studies not being published, or only selected data from a study being published, such as only the positive outcomes or only data from a subgroup with positive outcomes(140, 145). Publication bias may mean that effect sizes are overestimated, as the published papers do not form a representative sample of all the studies performed(146). It is unclear if the risk of reporting bias is greater for non-randomised studies(140). However, the risk is likely greater for studies without pre-specified protocols, such as retrospective studies(140). Four studies included in this review were retrospective (table 10, section 3.2)(112, 134-136). For two further studies it was unclear if they were prospective or retrospective(127, 128).

3.3 Primary outcomes

Seven studies reported fixed follow-up durations for all included patients at six(113, 135), 12(127, 130, 135, 138) or 24 months of follow-up(137). Seven studies reported either a mean, median or range of follow-up durations between 6.0 and 13.6 months(112, 128, 129, 131-134, 136).

3.3.1 Change in LVEF to greater than 35%

Two studies reported on change in LVEF to greater than 35% (table 16)(113, 137). Guerra et al reported change in LVEF at six months, at which point 25.2% of patients had an LVEF greater than 35% (table 16)(113). Paolini et al additionally reported echo outcomes at three, 12 and 24 months after starting sacubitril/valsartan (table 16)(137).

A third study reported on change in ICD eligibility, though did not report specifically on the proportion of patients with LVEF greater than 35% (table 16)(136). In this study, 40% of patients were no longer eligible for an ICD after a median follow-up of 11 months(136). This study was performed in Italy and as discussed in section 1.5, the ESC guidelines only recommend a complex device for HFrEF patients with NYHA II to IV symptoms(3). The study authors commented on this stating, "the main reason was LVEF increase rather than NYHA class improvement alone"(136).

Table 16: Change in proportion of patients with LVEF greater than 35% and no longer eligible for an ICD

Time on sacubitril/valsartan	**Proportion of patients with LVEF greater than 35%**		**Proportion of patients no longer eligible for ICD**
	Guerra 2021(113)	Paolini 2021(137)	Monzo 2021(136)
Three months		1.9%	
Six months	25.2%	21.2%	
Twelve months		38.5%	40.0%
Twenty-four months		46.2%	

ICD - implantable cardioverter-defibrillator, LVEF - left ventricular ejection fraction

Several factors may contribute towards the different proportions of patients no longer considered eligible for a primary prevention ICD in these three studies(113, 136, 137). Firstly, the sample size varied between the studies, from 48 participants in Monzo et al(136), 69 participants in Paolini et al(137) to 230 participants in Guerra et al(113). Smaller sample sizes may affect precision in the effect size estimated due to larger surrounding confidence intervals(143).

Secondly, the three studies had different rates of attrition, at 25% in Paolini et al, 13% in Monzo et al and 2% in Guerra et al (see table 15, section 3.2.3.3)(113, 136, 137). Patients lost to follow-up or not adhering to the study protocol were not included in the final analysis for any of these three studies(113, 136, 137). Missing data may introduce bias depending on the reason why it is missing(142). In Paolini et al, the commonest reasons for attrition were death or advanced heart failure treatment (orthotopic heart transplant or the implantation of a left ventricular assist device), which occurred in 8.7% of the population(137). Such survivorship bias may overestimate the improvements in LVEF reported by Paolini et al, as mortality and need for advanced heart failure treatment would usually be more likely in patients with persistent HFrEF(10). Unfortunately, Paolini et al do not report the LVEF of patients at the time of these adverse events(137). The relevance of survivorship bias to decisions around delaying ICD implantation will depend on the mode of death, as ICDs only able to reduce SCD secondary to ventricular arrhythmias. The mortality rate in Guerra et al was lower at 1.7% and no patients required advanced heart failure therapy(113). However, Guerra et al only followed-up patients for six months, compared to two years in Paolini et al(113, 137). Neither study specified the timepoints at which patients died. These two studies also differed in the proportions of patients with an ICD at baseline. In Guerra et al, all patients had an ICD at baseline, whereas in Paolini et al only 42.3% of patients had either an ICD or a CRT-D(113, 137). It is not clear if this affected mortality rates as Paolini et al did not specify if death occurred in patients with or without an ICD or CRT-D(137). Neither study reported mode of death(113, 137). Monzo et al reported mortality of 0% after a median follow-up duration of 11 months (IQR 6-14)(136). However, this study was conducted retrospectively, and it is not clear if any patients were not included due to death prior to a follow-up assessment of LVEF being performed(136). However, the authors did report attrition for other reasons, excluding 13% of patients from the final analysis due

to intolerance to sacubitril/valsartan(136).

Thirdly, two studies excluded patients with a CRT device(113, 136), whereas in Paolini et al CRT 'non-responders' comprised 11.5% of the cohort(137). However, Paolini et al did not report either the time between CRT implant and inclusion in the study or the criteria to classify patients as CRT 'non-responders'(137). As discussed in section 2.1.3, variable timepoints have been suggested for judging CRT response rates from three months to two years(50, 52, 101). Delayed response to CRT could explain the higher proportions of patients demonstrating LV remodelling in Paolini et al(137), compared to Monzo et al(113, 136).

3.3.2 LVEF increase of 5% or more

Three studies reported on absolute increase in LVEF of 5% or more in individual patients (table 17)(112, 113, 137). Guerra et al reported change in LVEF after six months of sacubitril/valsartan(113). 50.4% of patients showed an improvement in LVEF of 5% or more(113). 10.6% of the total cohort showed an improvement in LVEF of 10% or more(113). Martens et al reported change in LVEF for 73% of their cohort after an average follow-up duration of 364 days(112). In this group, 44% showed an improvement in LVEF of 5% or more(112). Paolini et al reported change in LVEF at several different timepoints during follow-up(137). The proportion with an increase in LVEF of 5% or more was 3.8% after three months, 25.0% after six months, 50.0% after 12 months and 57.7% after two years of sacubitril/valsartan(137).

Table 17: Proportion of patients with improvement in LVEF of 5% or more

Time on sacubitril/valsartan	**Proportion of patients with improvement in LVEF of 5% or more**		
	Guerra 2021(113)	Paolini 2021(137)	Martens 2019(112)
Three months		3.8%	
Six months	50.4%	25.0%	
Twelve months		50.0%	44%
Twenty-four months		57.7%	

LVEF - left ventricular ejection fraction

3.4 Secondary outcomes

3.4.1 Mean change in LVEF

Thirteen studies reported on mean change in LVEF after three to twenty-four months of sacubitril/valsartan (table 18).

Table 18: Mean LVEF after starting sacubitril/valsartan

Study	**Baseline LVEF mean (SD, range)**	**Mean LVEF (SD)**				
		3 months	**6 months**	**9 months**	**12 months**	**24 months**
Cemin 2023(133)	31 (23-34)				34 (7)	
Corrado 2022 - low dose ARNI(129)	31 (0.11)				33 (7)	
Corrado 2022 - high dose ARNI(129)	28 (0.05)				33 (4)	
Correale 2020(127)	34.0 (9.2)				39.5 (9.8)	
Frey 2021(134)	26.8 (5.4)				39.2 (10.0)	
Giallauria 2020(130)	28 (5.8)				31.8 (7.3)	
Gioia 2022(128)	29 (6)		34 (6)			
Guerra	28.3 (5.6)		32.2 (6.5)			

2021(113)						
Malfatto 2020(135)	30.1 (4.9)		32.2 (5.4)		35.3 (6.1)	
Monzo 2021(136)	30.0 (3.8)				33.9	
Paolini 2021(137)	28.5 (6.2)					38.2 (8.6)
Romano 2019(131)	27 (5.9)			30 (7.7)		
Russo 2022(138)	28.7 (4.6)				31.2 (4.2)	
Vitale 2019(132)	27.0 (6)		29.7 (7)			

ARNI - angiotensin receptor blocker/neprilysin inhibitor, LVEF - left ventricular ejection fraction, SD - standard deviation

In five studies mean LVEF increased by 5% or more between baseline and follow-up(127, 128, 134, 135, 137).

The reasons for five studies reporting greater improvements in mean LVEF compared to the other nine studies are not entirely clear. Follow-up duration does not appear to be consistently related to mean change in LVEF either. Whilst follow-up duration in one of the five studies with the greatest improvement in mean LVEF, Paolini et al(137), was longer than the others at 24 months, the improvement in mean LVEF was similar to shorter duration studies. For the other four studies with the greatest reported improvement in mean LVEF(127, 128, 134, 135), follow-up durations varied from six to twelve months, which was similar to the nine studies(112, 113, 129-133, 136, 138) reporting lesser degrees of improvement in mean LVEF. However, the five studies with the greatest improvement in mean LVEF(127, 128, 134, 135) differ from the other nine studies(112, 113, 129-133, 136, 138) in terms of sample size and attrition rate. The five studies have sample sizes lower than the mean of 109 patients (table 10, section 3.2)(127, 128, 134, 135, 137). Additionally, these

five studies reported higher rates of loss to follow-up than most of the others (table 15, section 3.2.3.3)(127, 128, 134, 135, 137). The attrition rate by 12 months in Malfatto et al is particularly high at 37%(135). Smaller sample sizes and higher attrition limits confidence in the results.

3.4.1.1 Discrete versus continuous change in LVEF

The significance of mean improvements in LVEF for complex device eligibility is not clear as mean improvements do not tell us how many patients in these studies have crossed the threshold of an LVEF greater than 35%. Comparing the change in mean LVEF to the change in ICD eligibility suggests heterogeneity between populations in each study cohort. As discussed in section 3.3.1, three studies reported a change in primary prevention ICD eligibility, which was predominantly driven by an improvement in LVEF to greater than 35%(113, 136, 137). The proportion of patients that were no longer considered eligible for an ICD was similar across these three studies (table 16, section 3.3.1). However, the mean change in LVEF varied between these studies (table 18)(113, 136, 137). Whilst follow-up duration was longer in Paolini et al, the authors reported on mean change in LVEF at earlier timepoints(137). Unfortunately, exact figures are not reported as the results are only presented graphically(137). However, the graph shows that most of the improvement in mean LVEF occurs by six months(137). The differences between studies suggest that overall mean change in LVEF does not fully explain the proportions of patients reaching the threshold of greater than 35%. It may be that improvements in LVEF are not equal between different patients.

Table 18: Mean changes in LVEF for studies reporting changing ICD eligibility

Study	Mean baseline LVEF (SD) (%)	Mean change in LVEF (%)	Follow-up duration (months)
Guerra 2021(113)	28.3 (5.6)	3.9	6
Monzo 2021(136)	30.0 (3.8)	3.9	11 (median)
Paolini 2021(137)	28.5 (6.2)	9.7	24

ICD - implantable cardioverter-defibrillator, LVEF - left ventricular ejection fraction, SD - standard deviation

3.4.2 Mortality and hospitalisation

Six studies reported on mortality (table 20)(113, 131, 133, 136-138). The mortality rate was 0% in two studies(131, 136), one of which was conducted retrospectively(136). In the remaining four studies mortality varied between 1.7% and 7.6%, though this does not appear to be consistently related to follow-up duration (table 20)(113, 133, 137, 138). The differing proportions of patients with an ICD (or CRT-D) may be relevant, as lower mortality was reported in the three studies in which all patients had one of these devices(113, 136, 138). Monzo et al, which only included patients with an ICD at baseline, reported 0% mortality in their study(136). However, this study was conducted retrospectively, and it is not clear if any patients were not included due to death prior to a follow-up assessment of LVEF(136). However, in the other two studies that only included patients with an ICD or CRT-D at baseline, mortality rates ranged between 1.7% after six months of follow-up in Guerra et al(113) and 2.6% after 12 months of follow-up in Russo et al(138). None of the studies reported on the mode of death.

Five studies reported on heart failure hospitalisation (table 20). The heart failure hospitalisation rate was 0% in one study(136). In the remaining four studies, heart failure hospitalisation varied between 0.9% and 19.5% (table 20)(131, 133, 137, 138).

Table 20: Mortality and heart failure hospitalisation

Study	**Follow-up duration (months)**	**Mortality (%)**	**Heart failure hospitalisation (%)**
Guerra 2021(113)	6	1.7	Not reported
Romano 2019(131)	10.5 (median, range 2.9-18.4)	0	0.46
Monzo 2021(136)	11 (median, IQR 6-14)	0	0
Russo 2022(138)	12	2.6	19.5
Cemin 2023(133)	13.6 (mean, SD not reported)	7.6	19.0
Paolini 2021(137)	24	4.3	5.8

IQR - interquartile range, SD - standard deviation

3.4.3 ICD therapy

Three studies reported on ICD shock rates, which varied from 5.3% at six months(113), to between 4.0% and 6.3% at 12 months(112, 138) (table 21). In two of these studies, all the patients had either an ICD or a CRT-D(113, 138). In the third study, only 81.4% of patients had an ICD or CRT-D, with the remainder having a CRT-P(112). However, this third study additionally reported ventricular arrhythmias separately to ICD therapy(112)(table 21). Nevertheless, it should be noted that only one of these studies was explicitly in a primary prevention ICD population(113). In Russo et al it was unclear whether the indication for a defibrillator was for primary or secondary prevention(138). In Martens et al, the cohort included a combination of patients with each indication, though the exact proportions of each were not specified nor were the ICD therapy rates or ventricular arrhythmia rates reported by each subgroup(138). ICD therapy rates tend to be higher in patients with a secondary prevention indication(147), which limits the applicability of these results to a primary prevention population.

Furthermore, all three studies included patients who were prescribed the antiarrhythmic drug amiodarone(112, 113, 137, 138). A fourth study, which reported mortality but not ICD therapy also included patients prescribed amiodarone(112, 113, 137, 138) (table 20). The proportions of patients prescribed amiodarone varied from 17% to 33% of patients(112, 113, 137, 138). Whilst Guerra et al reported no difference in the rates of appropriate ICD shocks between patients prescribed or not prescribed amiodarone(113), other studies have reported significantly lower rates of both ICD therapy and SCD in patients with HFrEF treated with this drug(148). Amiodarone use in these studies may mean that both ICD therapy rates and/or SCD rates are lower than would otherwise be expected.

Table 21: ICD therapy and ventricular arrhythmias

Study	Follow-up duration (months)	Proportion of patients with ICD or CRT-D (%)	Proportion of patients receiving one or more appropriate ATP/shock(s) (%)	Proportion of patients with one or more episode(s) of sustained ventricular arrhythmia (%)
Guerra 2021(113)	6	100	5.3	
Russo 2022(138)	12	100	6.3	6.3
Martens 2019(112)	12	81.4	4.0	6.6

ATP - anti-tachycardia pacing, CRT-D - cardiac resynchronisation therapy-defibrillator, ICD - implantable cardioverter-defibrillator

3.4.4 Follow-up drug doses

Ten studies reported on sacubitril/valsartan doses at follow-up (table 22)(113, 128-135). One study reported mean dose, which was 56% (+/-27%) of the maximum(112).

Table 22: Proportion of patients on percentage maximum dose of sacubitril/valsartan

	Percentage of maximum dose of sacubitril/valsartan		
Study	**25%**	**50%**	**100%**
Cemin 2023(133)	20%	36%	43%
Corrado 2022(129)	58%	42%	
Frey 2021(134)		11%	89%
Giallauria 2020(130)	29%	36%	35%
Gioia 2022(128)	51%	34%	15%
Guerra 2021(113)	28%	42%	30%
Malfatto 2020(135)	6%	51% (50-75% max)	43%
Romano 2019(131)	39%	34%	27%
Vitale 2019(132)	28%	38%	34%

Five studies examined the effect of different doses of sacubitril/valsartan on change in LVEF(129, 130, 136-138). Two studies reported mean LVEF by sacubitril/valsartan dose(129, 130). Corrado et al reported subgroups of patients on low dose sacubitril/valsartan (defined as less than or equal to 75mg twice a day) and high dose (defined as more than 75mg twice a day)(129). The difference in mean LVEF improvement between these two subgroups was not statistically significant(129). Giallauria et al reported three subgroups based on low (50mg twice a day), middle (100mg twice a day) and high dose (200mg twice a day) sacubitril/valsartan(130). Mean LVEF was reported as 29.2%+/-7.2 (low subgroup), 32.1%+/-6.5 (middle subgroup) and 33.8%+/-8.0 (high subgroup)(130). The improvement in LVEF was reported as significant for the middle and high dose subgroups. Three other studies used regression analysis to examine the impact of sacubitril/valsartan dose on change in LVEF(136-138). One study found patients were more likely to improve if they were on a dose greater than 50mg twice a day(136). Higher doses of sacubitril/valsartan were not associated with greater improvements in LVEF in either of the other two studies(137, 138).

3.5 Subgroup analysis

Subgroup analysis was pre-specified for three sample characteristics (see section 2.5). As all the studies were of patients switching to sacubitril/valsartan from the maximum tolerated

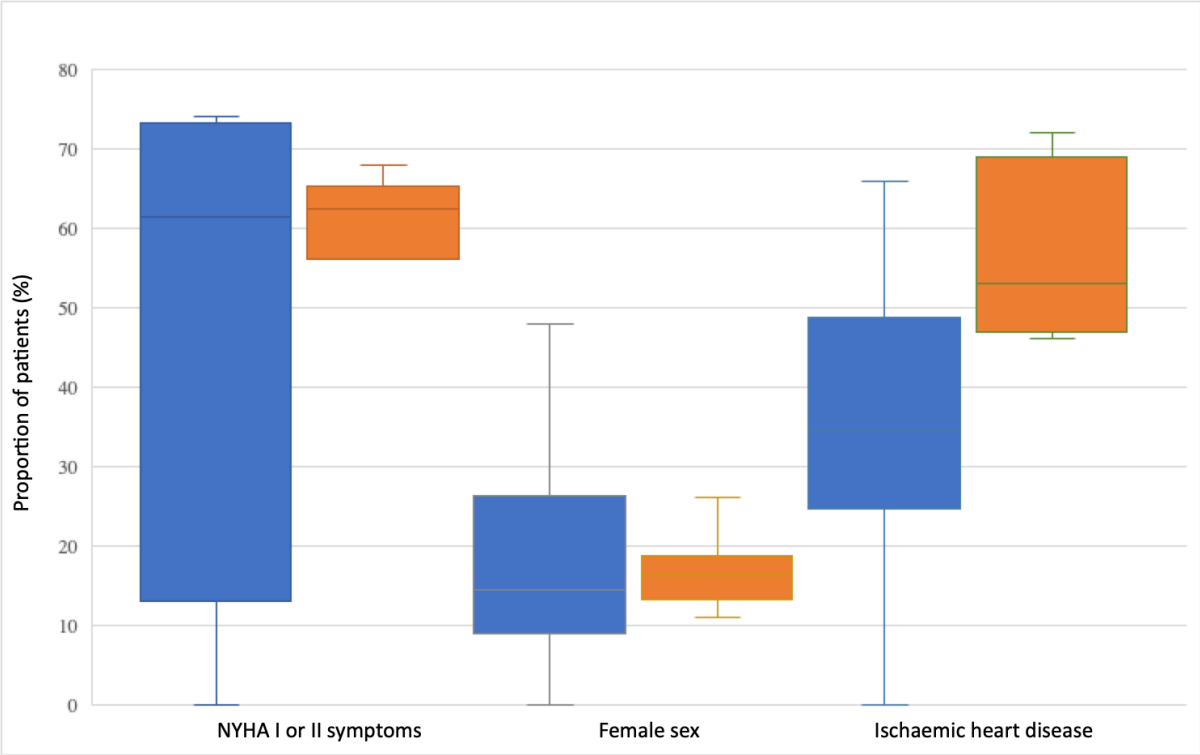
dose of ACE inhibitor or ARB, subgroup analysis by baseline medical treatment was not possible. However, subgroup analysis by presence of CRT and aetiology of heart failure was possible. Additionally, four studies also reported their own regression analyses to find predictors of LV remodelling(113, 136-138).

Baseline LVEF does not appear to be consistently related to the mean observed change in LVEF during follow-up. Of the four studies that performed regression analysis to find predictors of LV remodelling, two studies reported that a lower baseline LVEF was associated with a greater improvement in LVEF(113, 138). However, this does not fully explain the differences between studies. The baseline LVEF was highly variable between the five studies that reported the greatest improvement in mean LVEF and was not consistently lower than the other nine studies (table 18, section 3.4.1). Follow-up duration does not appear to be consistently related to mean change in LVEF either. Whilst follow-up duration in one of the five studies with the greatest improvement in mean LVEF, Paolini et al(137), was longer than the others at 24 months, the improvement in mean LVEF was similar to shorter duration studies. For the other four studies(127, 128, 134, 135) with the greatest reported improvement in mean LVEF, follow-up durations varied from six to twelve months, which was similar to the nine studies(112, 113, 129-133, 136, 138) reporting lesser degrees of improvement in mean LVEF.

One study reported that NYHA class II compared to class III was associated with a higher probability of improvement in LVEF(136). Another study reported that female sex was associated with a higher probability of remodelling(137). Age and past medical history of AF were not associated with a difference in the probability of improvement in LVEF in the four studies reporting analysis of these variables(113, 136-138).

If we compare the five studies included in the review with the greatest improvement in mean LVEF(127, 128, 134, 135, 137) with the other nine included studies(112, 113, 129-133, 136, 138), no consistent pattern was seen in the proportions of female patients, proportions of patients with IHD or the proportions of patients with NYHA class I or II symptoms at baseline(figure 4).

Figure 4: Box and whisker plot comparing proportions of patients with NYHA I to II symptoms, female sex and IHD in studies reporting a mean improvement in LVEF of 5% or more, compared studies reporting mean improvement in LVEF of less than 5%



Boxes showing median and interquartile range, whiskers showing maximum and minimum values. Blue – Five studies reporting mean improvement in LVEF of 5% or more(127, 128, 134, 135, 137)*. Orange – Nine studies reporting mean improvement in LVEF of less than 5%*(112, 113, 129-133, 136, 138)*.*

IHD - ischaemic heart disease, LVEF - left ventricular ejection fraction, NYHA - New York Heart Association

3.5.1 CRT versus no CRT

As stated in section 3.2.2.9, 11 studies included differing proportions of patients with CRT, ranging from 11.5% to 100%(112, 128-135, 137, 138). Studies varied in their criteria for including patients with CRT at baseline, from setting a specific duration of time since implant to requiring patients to be CRT 'non-responders'. However, as discussed in section 2.1.3, CRT can cause LV remodelling and there is no consensus on the duration of CRT before the maximum extent of LV remodelling is seen. This may influence the effect size seen and makes direct comparisons between studies more difficult.

Two studies excluded patients with CRT at baseline (113, 136). In two studies, more than 50% of patients had a CRT at baseline(112, 138). In Russo et al, all the patients had a CRT, though were only included if they were non-responders to CRT. This was defined as a reduction in LVESV of less than 15% after 12 months of CRT despite a biventricular pacing rate of at least 95%. In Martens et al, 69.9% of patients had a CRT and were included provided their LVEF remained 35% or less after six months of CRT.

In the two studies that excluded patients with CRT, mean LVEF increased by 3.9% in both studies, though the follow-up duration differed between these studies, being six months in one study(113) and 12 months in the other study(136). In Russo et al, where all patients had a CRT at baseline, mean LVEF increased by 3%(138). Martens et al, where 69.9% of patients had a CRT at baseline, did not report change in mean LVEF(112). Martens et al reported the proportion of patients whose LVEF improved by more than 5%, which was 44% after 12 months(112). This compares to 50% of patients after just six months in Guerra et al, which excluded patients with CRT(113).

3.5.2 Aetiology of heart failure

One study reported outcomes separately for patients with ischaemic vs non-ischaemic aetiology for their heart failure(133). The authors found a significant improvement in mean LVEF in the subgroup of patients with a non-ischaemic aetiology, but not in those with an ischaemic aetiology(133). There was no difference in mortality or heart failure hospitalisation between the subgroups(133). However, baseline characteristics differed between the subgroups with a higher proportion of male patients, higher serum creatinine, greater prevalence of NYHA class III (compared to class II), but a lower prevalence of AF in the ischaemic aetiology subgroup(133).

As discussed above, four studies performed regression analysis to identify predictors of LV remodelling(113, 136-138). Two of these reported a higher probability of patients' experiencing an improvement in their LVEF improving by 5% or more in the subgroup with a non-ischaemic aetiology(113, 137). However, two studies reported no difference in LV

remodelling between subgroups with an ischaemic versus a non-ischaemic aetiology for heart failure(131, 138).

Chapter 4. Discussion

The objective of this review was to explore rates of delayed LV remodelling in patients with HFrEF treated with OMT. In particular, I sought to answer the question of whether delayed remodelling affects eligibility for ICDs and CRT as determined by NICE guidelines(12). The secondary aims were to explore rates of mortality and ICD therapy in patients with persistent HFrEF despite at least three months of OMT.

4.1 Summary of the main results

This synthesis collated data from 14 cohort studies, which included a total of 1456 patients. The studies were published between 2019 and 2023. All of the studies were conducted in Europe and reported on patients with HFrEF that were newly prescribed the ARNI, sacubitril/valsartan. At baseline all patients had an LVEF of 35% or less despite at least three months of OMT, which included the maximally tolerated dose of either an ACE inhibitor or an ARB. All 14 studies reported some degree of LV remodelling after patients were prescribed sacubitril/valsartan, although the reporting methods and degree of improvement differed between studies.

4.1.1 Complex device eligibility

Three studies reported on the proportion of patients that experienced a change in their LVEF to greater than 35% and/or reported on change in ICD eligibility(113, 136, 137). In the two studies that reported a change in LVEF to greater than 35%, the proportion of patients that reached this threshold was 21.2%(137) and 25.2%(113), after six months of sacubitril/valsartan. Paolini et al also reported that 39% of patients had an improvement in their LVEF to greater than 35% after 12 months of sacubitril/valsartan(137). The third study did not specifically report the proportion of patients with an LVEF greater than 35%(136). Instead, the authors reported change in primary prevention ICD eligibility, which in the ESC guidelines is determined by NYHA class as well as LVEF(3, 136). However, the authors note that "the main reason [for patients no longer being eligible] was LVEF increase rather than NYHA class improvement alone"(136). In this study, 40% of patients were no longer considered eligible for a primary prevention ICD after a median follow-up of 11 months(136), which is similar to the proportion of patients in Paolini et al's study whose

LVEF improved to greater than 35% after 12 months of sacubitril/valsartan(136, 137).

The implications for CRT eligibility are not entirely clear from this review. CRT eligibility at baseline was not reported by any of the included studies, and only one study reported the proportion of patients with a CRT at both baseline and follow-up(130). The proportion of patients with a CRT in the included studies was variable (see section 3.2.2.9). This may suggest that many patients were not eligible for CRT, although there is some evidence that CRT is currently underutilised in eligible patients with HFrEF(139).

4.1.2 Mean change in LVEF

Thirteen studies reported a mean change in LVEF, which increased between 2.0% and 12.4% after between six and 24 months of sacubitril/valsartan(113, 127-138). Five studies reported an increase in the mean LVEF across their whole cohort by 5% or more(127, 128, 134, 135, 137).

4.1.3 Mortality rates and ICD shock rates

Mortality rates ranged from 0% to 7.6%, and was reported in only six studies(113, 127, 131, 133, 136-138). ICD therapy rates also varied, ranging from 3.7% to 7.4%(112, 113, 138). However, ICD prevalence also varied (between 28.6% and 100% at baseline)(112, 113, 127-138) and ICD therapy rates were only reported in three studies(112, 113, 138).

4.2 Strengths and limitations of the evidence

All 14 studies included in this review were observational, single cohort studies. The inclusion of observational studies was justified as no randomised control trials were found that met the inclusion criteria. However, non-randomised studies inherently carry a higher risk of bias than randomised studies, which necessitates greater caution in interpreting their results(149). Non-randomised studies have a higher risk of confounding, due to the lack of randomisation, and interpreting causality is more challenging(149). However, the inclusion of non-randomised studies is justified as no randomised studies were available(149). Furthermore, the included non-randomised studies directly address the review question and none of the studies have a critical risk of bias (see table 13, section 3.2.3)(149).

4.2.1 Differences in ICD eligibility and change in LVEF more than 5%

As discussed in section 3.3.1, only three studies reported changes to ICD eligibility(113, 136, 137). This reduces confidence in the reported effect size as this variable was only reported for 347 patients (out of a possible 1456 patients across all of the included studies). Furthermore, only three studies (totalling 416 patients) reported the proportion of patients whose LVEF increased by more than 5%(112, 113, 137). Additionally, reproducibility of LVEF assessments may impact on the accuracy of the effect size reported. As discussed in section 3.2.3.2, inter-observer variability in LVEF assessments using TTE, though small in the studies that reported it (between 3.4% and 5.2%), was similar to the mean change in LVEF reported by most of the included studies. Furthermore, other studies examining reproducibility of TTE assessments of LVEF have reported even greater inter-observer variability(120, 121). Even with a lower than expected variability in LVEF assessments in the included studies which reported it, this degree of variability is a significant limitation. It is more important when a relatively small change in LVEF is considered clinically significant, such as a change in LVEF of more than 5% or a change in LVEF to greater than 35% (which may represent a very small absolute change in LVEF depending on the baseline measurement, e.g. a change from 34% to 36%). Additionally, the impact of inter-observer variability may simply be higher when assessing a binary change in LVEF. However, I have not found any data, either in the included studies or in the wider literature, to suggest higher LVEF values are preferentially reported when a particular LVEF threshold is being considered.

4.2.1.1 Differences in CRT eligibility

The implications for CRT eligibility are not clear from this review. CRT eligibility at baseline was not reported by any of the included studies. Therefore, it is not clear whether this review's findings can be applied to a population of patients with HFrEF who are eligible for a CRT.

4.2.2 Differences in mortality and ICD therapy rates

Any consideration of delaying ICD (or CRT-D) implantation needs to take account of the mortality risk in doing so. However, there are limitations in the mortality data in this review. Firstly, mortality rates varied in the six included studies that reported this outcome(113,

131, 133, 136-138) and the reasons for differences are not clear. Secondly, the mortality rates reported by the included studies are much lower than other recent heart failure studies. For example, in the placebo group in DAPA-HF, the mortality rate was 13.5% over the course of a mean follow-up duration of 18.2 months(65). Thirdly, and perhaps most importantly, none of the studies reported the mode of death. This is important to note as ICDs can only prevent SCD secondary to ventricular arrhythmias, but not other modes of death including other modes of SCD, such as acute pump failure(150). Using all-cause mortality will likely overestimate the impact of ICDs.

ICD therapy rates may give a better indication of the likely risk associated with delaying ICD implantation. However, there are also limitations in the included studies that reported ICD therapy rates. Firstly, only three studies reported on ICD shock rates, meaning that this important outcome data is only available for 39% of the total patient population across the included studies. Secondly, only one of these studies was explicitly in a primary prevention ICD population(113), with the other studies either including an unknown number of patients with a secondary prevention ICD or not stating whether the patients had a primary or a secondary prevention device(112, 113, 138). As ICD therapy rates tend to be higher in patients with a secondary prevention indication(147), the applicability of these results to our primary prevention population is reduced. Thirdly, none of the studies reported their ICD programming strategies(112, 113, 138). ICD therapy rates depend not only on the patient population, but also on how the devices are programmed. If ICDs are programmed to deliver therapy early, they may deliver unnecessary therapy for self-resolving arrythmias(26, 28, 31, 32, 32).

4.2.3 Subgroup analysis

As discussed in section 3.5, only one study reported outcomes separately for patients with ischaemic versus non-ischaemic aetiology for their heart failure(133). Additionally, in this study several potentially prognostically significant baseline characteristics varied between these two subgroups, which limits the conclusions that can be made from aetiology alone(133). Additionally, the four studies performing regression analysis to assess predictors of LV remodelling reported conflicting results regarding the impact of an ischaemic versus

non-ischaemic aetiology for heart failure(113, 136-138).

Subgroup analysis for the other pre-specified subgroups (baseline medical therapy and baseline CRT) was not possible based on the data reported in the included studies.

4.2.4 SGLT2 inhibitors

None of the included studies included patients that were prescribed SGLT2 inhibitors. As discussed in section 1.2, SGLT2 inhibitors are currently recommended as part of OMT for patients with HFrEF(3, 151). However, the included studies were all conducted before SGLT2 inhibitors were licensed for HFrEF. Whilst a recent systematic review found no impact of SGLT2 inhibitors on LV remodelling(111), another found that SGLT2 inhibitors reduced both all-cause and cardiovascular mortality in patients with HFrEF that were also prescribed sacubitril/valsartan(152). This becomes relevant when considering the mortality rates in the included studies, as this may have been lower had patients been prescribed SGLT2 inhibitors in addition.

4.3 Strengths and limitations of the review

4.3.1 Search strategy

The initial search strategy was revised as initial strategies returned more than 20,000 articles, which was too many to be feasible to review within the timeframe available. Early attempts at using the filtering options by study type in MEDLINE and EMBASE reduced the number of matches to a feasible number, but excluded studies that were known to be eligible based on scoping searches. Relevant studies identified by scoping searches could have been added manually, but continuing with this search strategy could have missed other relevant studies and potentially introduced bias.

Therefore, an alternative strategy was developed, which incorporated study type search terms into the search itself (see appendix 1)(153). Studies that were not published in English were also excluded, which may limit the generalisability of the findings(154). The included citations were also limited by time to ensure that sacubitril/valsartan was a treatment option for patients that were included in the studies. The rationale for this decision was

primarily to make the results more clinically relevant to contemporary practice. Sacubitril/valsartan is currently recommended for patients with HFrEF if they have not remodelled on an ACE inhibitor (or ARB depending on the guideline followed), though continued ACE inhibitor (or ARB) is still recommended if patients do not tolerate sacubitril/valsartan(3, 8). Studies of patients prior to the availability of sacubitril/valsartan would not reflect current guidelines, and inclusion of these studies would have posed significant challenges to synthesis. However, this strategy appears to have limited the review to only include patients that were prescribed sacubitril/valsartan as no eligible studies were included with patients that remained on ACE inhibitor or ARB. Consequently, the findings cannot necessarily be applied to patients who remain on ACE inhibitor or ARB due to intolerance to sacubitril/valsartan.

4.3.2 Eligibility criteria

The requirement for study patients to have been prescribed OMT for at least three months at baseline restricted the included studies significantly. A large number of studies used the inclusion criteria from PARADIGM-HF of a minimum of four weeks of ACE inhibitor or ARB before switching to ARNI(64). These studies were therefore excluded from the review unless other information was provided regarding the duration of OMT at baseline. This decision was made to ensure that we assessed delayed rather than early remodelling. However, as the four-week criterion was a *minimum* duration, many patients in these excluded studies may have been on OMT for longer than this. Unfortunately, it was not possible to factor this in without access to individual patient data, which, given the large number of studies involved, was not feasible within this review.

4.3.3 Overlap between included studies

As discussed in section 3.1.2, six of the included studies contained potentially overlapping cohorts of patients(127-132). The authors of these studies did not respond to requests to clarify whether any overlap was present. Potentially overlapping cohorts mean that the total number of individual patients within the review is likely to be lower than stated, though unfortunately the degree to which this is the case is unclear. This was part of the reasoning behind not performing a meta-analysis, as this would have incurred the risk of including the

same patient's data more than once, thus introducing bias. However, for a narrative synthesis, the risks of this altering the findings significantly are low. The reported effect sizes in the studies with potential overlap do not appear to be significantly different to the other studies. Additionally, none of these six studies reported on either of the primary outcomes.

4.3.4 Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess risk of bias(116). However, there are issues with this scale. Firstly, the scale required modification as none of the included studies had a comparison cohort. This meant that the domain 'comparability', was not relevant, nor was the question regarding selection of the non-exposed cohort in the 'selection' domain. This created issues in using a summary score to assess overall risk of bias using the Agency for Healthcare Research Quality (AHRQ) categories(116).

Secondly, several authors have questioned the validity and/or reliability of the NOS(118, 155, 156). Both Hartling et al(155)and Lo et al(156) assessed the interrater reliability of the NOS. Both papers found low reliability in several NOS domains(155, 156). Of particular relevance to this review, slight or poor reliability was found for adequacy of follow-up, which was one of the domains with the largest variation between the studies included in this review (see table 13, section 3.2.3)(155, 156). Additionally, slight or fair reliability was found for representativeness of the cohort, which again was an area of difference between the studies included in this review(155, 156). Lo et al also found poor reliability for the overall NOS, which only improved to slight reliability when the overall scores were categorised as low risk, high risk or very high risk(156). Stang(118) also questioned the validity of the NOS domains about representativeness of the cohort. Stang argued that studies could introduce a different bias by ensuring their cohorts were representative of the wider population if in seeking a more representative cohort, studies would introduce a lower response rate(118). This would result in a different selection bias to recruiting a less representative cohort, but with a higher response rate. For example, most of the studies included in this review included a majority of male patients, which does not represent the overall heart failure population, which is more evenly divided between male and female. However, if study authors sought to recruit a population with equal male and female

participants, this might take longer to recruit. This could result in a greater number of eligible participants being excluded to avoid skewing the population characteristics, which itself could introduce bias(118). It would perhaps be better to consider representativeness of a study's cohort in terms of applicability of the results to a wider population, rather than in terms of selection bias.

Stang also highlights the issue of using NOS summary scores(118). The example Stang gives is for the assessment of outcome domain(118). In this domain, assessment of outcome by either independent blind assessment or record linkage are given the same weighting in the overall risk of bias score, despite these two methods clearly being different. As discussed in section 3.2.3.2, unblinded assessment of LVEF could influence the key review findings. Jüni et al also criticised the use of summary scores to assess quality, given this can hide heterogeneity between studies(117). In this review, I sought to assess different aspects of bias individually and relate this to the relevance to study outcomes.

For this review, studies were not included or excluded based on their risk of bias. Instead, the risk of bias assessment has been used to consider reliability and applicability of results. Therefore, the limitations of NOS only have a small impact on the review's conclusions.

4.4 Results in the context of the wider literature

4.4.1 Comparing included studies to the wider population of patients with HFrEF

To understand the extent to which the included studies were representative of the population of patients with HFrEF encountered in clinical practice, and therefore the extent to which the study results are applicable to this wider population, I have compared the study cohorts to those reported in national audit and registry data. Unfortunately, the largest audit data of UK patients with heart failure, which is available from the National Heart Failure Audit (NHFA), does not report demographics or outcomes for the subgroup of patients with HFrEF as distinct from the broader population of patients with heart failure(6). As the clinical characteristics and prognoses vary significantly between patients with differing severities of systolic dysfunction(3), an alternative dataset was required for comparisons to the study cohorts. Therefore, comparison was made with patients in SwedeHF, a large registry of patients with heart failure in Sweden from which data on more

than 36,000 patients with HFrEF has been reported(141). However, it should be noted that registries are also subject to selection bias, though the extent and significance of selection bias is often challenging to determine(157). One comparison of SwedeHF to data collected from national coding data suggested selection bias in the SwedeHF registry(157). Nonetheless, there are limitations of this comparison due to missing data in the national coding dataset, and dependence on coding itself, which may contain errors(157, 158). Additionally, it should be noted that none of the studies included in the review were based in Sweden, which has an uncertain impact on the validity of using SwedeHF for comparison. However, all the included studies were conducted in Western Europe. Furthermore, 12 of the included studies were conducted in Italy, whose healthcare system, like Sweden, is financed through taxation as opposed to social insurance or out of pocket payments(159). Therefore, we would expect some similarities between Italy and Sweden in terms of the characteristics of the population of patients with heart failure and the HFrEF treatments utilised.

Considering the studies in this review, the cohorts in 13 studies were somewhat representative of the SwedeHF HFrEF population (table 13, section 3.2.3)(112, 113, 127-133, 135-138). However, these 13 studies included patients that were typically younger than the average patient with HFrEF in SwedeHF. The mean age of patients in these 13 studies was 62.9 years, compared to 73.3 years for patients with HFrEF in SwedeHF(141). Additionally, for these 13 studies, the proportion of male patients was 80% (range 73-87%), which is higher than the 71% of patients in SwedeHF who were male(141).

Comparisons of baseline characteristics that affect prognosis (see section 1.3) were also considered. Whilst these 13 studies' cohorts were similar to SwedeHF patients in terms of NYHA class, systolic blood pressure, eGFR and prevalence of IHD, differences were present in the prevalence of AF and baseline NT-proBNP levels. For example, one study excluded patients with AF(129) and two studies did not report the prevalence of AF amongst participants(127, 135). The median prevalence of AF in the remaining ten studies was 33% (range 8-41%)(112, 113, 128, 130-133, 136-138). This compares to 52% in the patients with HFrEF in SwedeHF(141). Additionally, mean NT-proBNP levels at baseline were higher in patients enrolled in SwedeHF than in most of the included studies(141). However, this may

reflect that medications had not yet been optimised at the point of patient enrolment in SwedeHF. SwedeHF did not require patients to be on OMT for inclusion, whereas this was an inclusion criterion for all of the studies in this review(112, 113, 127-138, 141). Both AF and higher NT-proBNP are adverse prognostic markers in patients with HFrEF (see section 1.3)(3, 14). By including fewer patients with AF and patients with lower mean NT-proBNP levels at baseline, the included studies may have underestimated negative outcomes such as mortality(112, 113, 127-133, 135-138). This may limit their applicability patients with HFrEF encountered in clinical practice.

For the remaining study included in this review, patients were drawn from a selected population of patients with HFrEF and a history of cancer(134). In SwedeHF, only 14.5% of patients had a history of cancer. As discussed in section 2.1.1, patients with chemotherapy-induced heart failure generally have a high rate of remodelling. However, in Frey et al, the aetiology of HFrEF was not stated and mean time from diagnosis of cancer to diagnosis of HFrEF was 5.8 years (0.2-24.3)(134). This suggests that there was likely to have been substantial heterogeneity within the cohort, which makes interpretation and application of the results more challenging.

4.4.2 Complex device eligibility

The three studies that reported the proportions of patients no longer considered eligible for a primary prevention ICD(113, 136, 137), all reported a similar proportions to another study that reported on change in ICD eligibility in patients with HFrEF treated with sacubitril/valsartan(72). PROVE-HF was a study of 794 patients with HFrEF (based on an LVEF of 40% or less) who were newly prescribed sacubitril/valsartan(72). The study was not included in this review as not all patients were on OMT at baseline(72). A later analysis of PROVE-HF examined outcomes in the subgroup of 661 patients with an LVEF of 35% or less at baseline(73). In this subgroup, latent growth curve modelling was used to analyse the proportion of patients that would no longer be considered eligible for a primary prevention ICD after six to twelve months of sacubitril/valsartan(73). The authors reported that 32% of patients had an improvement in their LVEF to greater than 35% after six months, which increased to 62% at 12 months(73). Similar numbers were reported if the analysis excluded patients that had an ICD or CRT-D at baseline (39% at six months, 75% at twelve

months)(73).

4.4.2.1 Time course of improvement

Of the three studies that reported change in ICD eligibility, only one reported on LVEF following different durations of sacubitril/valsartan(137). Paolini et al reported that 21.6% of patients had an LVEF of greater than 35% at six months, which rose to 38.5% of patients at 12 months(137) (see table 16, section 3.3.1). A further modest rise to 46.2% of patients with an LVEF of greater than 35% was reported at two years(137). A similar result was reported in an analysis of patients with HFrEF in the TAROT-HF registry, a multi-centre registry of patients with HFrEF based in Taiwan who were newly prescribed sacubitril/valsartan(160). Huang et al reported on the subgroup of patients with an LVEF of 35% or less and reported outcomes according to CRT eligibility at baseline(161). This paper provides context in the wider literature for change to both ICD and CRT eligibility at different durations of sacubitril/valsartan.

Huang et al's study was excluded from the review as not all patients were on OMT at baseline(160, 161). CRT eligibility was determined according to the ESC guideline criteria (see section 1.4.3)(3). In the subgroup considered eligible for CRT, there was LV remodelling to greater than 14.9% of patients after six months of sacubitril/valsartan(161). This proportion rose further to 32.3% after 12 months(161). Whilst this proportion is smaller than that seen in the included studies, it still represents a large minority of the population. However, it should be noted that in the CRT eligible subgroup, 8.7% of patients underwent CRT implant over the course of the study with a median time to implant of 159 days (range 91-347 days)(161). This does confound the results, as CRT itself can induce LV remodelling(50, 101). Nevertheless, even if all the CRT patients remodelled, this would still leave 23.6% of patients remodelling on OMT alone. Huang et al also report on their second subgroup, who were not eligible for CRT at baseline(161). Unfortunately, specific numbers are not reported, though a Kaplan-Meier graph is provided comparing the two groups(161). This demonstrates a higher proportion of patients demonstrating LV remodelling to an LVEF greater than 35% in the CRT ineligible subgroup compared to the CRT eligible subgroup(161). The proportions of patients demonstrating LV remodelling in the CRT ineligible subgroup was similar to the proportion reported in the studies included in the

review. As discussed in section 1.4.2, prognosis is poorer in patients with HFrEF if they are eligible for CRT(46). Additionally, several other observational studies have reported lower rates of LV remodelling in patients with HFrEF who have LBBB(162). As discussed in section 1.4.2, LBBB is one indication for CRT(3). Differences in LV remodelling on OMT between patients with HFrEF who are and are not eligible for CRT makes it difficult to apply this review's findings to patients that are eligible for CRT.

Huang et al also presented data graphically for remodelling beyond 12 months of sacubitril/valsartan(161), which, as with Paolini et al(137), suggested that most of the improvement in LVEF tends to occur by 12 months(137, 161). However, there is a large amount of missing data in Huang et al, with missingness increasing with treatment duration(161). At baseline, Huang et al reported data for 1,168 patients(161). For a change in LVEF to more than 35%, Huang et al only reported on 602 patients at one year (52%) and 410 patients at two years (35%)(161). The reasons for missing data are not reported and as such the impact on the reported change in LVEF is unclear.

One limitation of Huang et al's analysis is that patients were only included if they had a follow-up LVEF assessment(161). This limits certainty in the effect size due to selection bias and an unclear initial denominator. It is unclear from the published paper how data was dealt with for patients who died during follow-up(161). Whilst the authors note that mortality was more likely prior to LV remodelling, as LVEF outcomes were reported by follow-up duration, survivorship bias may have been introduced, which would potentially overestimate the effect size(161). Huang et al identified 1,544 patients with an LVEF of 35% or less at baseline, yet LV outcomes at 12 months were reported for only 1,168 patients (76%)(161). At timepoints beyond 12 months, the attrition rate was even higher(161).

4.4.3 Mortality and ICD therapy rates

As discussed above, the mortality rates in the included studies was lower than in the placebo group in DAPA-HF. Lower than expected mortality rates in the included studies suggest that their cohorts may not reflect the wider population of patients with HFrEF and thus the included studies may underestimate the mortality risk of delaying ICD implantation.

Additionally, none of the included studies specified SCD rates separate from all-cause mortality. However, insights into the rates of SCD compared to other modes of death in patients with HFrEF can be gained from the wider literature. A later analysis of PROVE-HF reported SCD in 0.8% of participants at 12 months amongst the subgroup of patients with an LVEF of 35% or below(73). All-cause mortality was much higher at 3.5% in this subgroup at the same time-point(73). This difference between rates of all-cause mortality and SCD in PROVE-HF(73) suggests we may overestimate the potential impact of ICDs if only the all-cause mortality rates reported in the included studies are considered.

In the subgroup of patients in PROVE-HF with an LVEF of 35% or less at baseline, all deaths occurred in the group of patients that had an improvement in their LVEF to greater than 35% during follow-up(73). This suggests that LVEF alone is insufficient to predict SCD. Earlier studies have also highlighted the limitations in using LVEF as a sole predictor of SCD(163, 164). However, whether sacubitril/valsartan reduces SCD separate to its effect on LV reverse remodelling is less clear. This question is challenging to answer, given a paucity of clear data in the literature. Whilst several studies have reported reductions in SCD and/or ventricular arrhythmias in patients with HFrEF prescribed sacubitril/valsartan, these studies have also reported improvements in LVEF and not reported the relationship between the two outcomes(165-167). However, a later analysis of the PARADIGM-HF trial reported that whilst sacubitril/valsartan reduced the rate of SCD in patients without an ICD, the greatest reduction in SCD was seen in patients with an ICD who were also prescribed sacubitril/valsartan(75). The authors suggest this effect could be explained by sacubitril/valsartan impacting different causes of SCD to ICDs(75). Separately, a meta-analysis of trials of Dapagliflozin (an SGLT2 inhibitor) in patients with heart failure reported a reduction in SCD irrespective of LVEF, though the patients with a lower LVEF were still at greater risk of SCD than patients with a higher LVEF(168).

The probability of SCD being preventable by an ICD appears to be associated with the individual's NYHA class(169). Iles et al found that the proportion of SCD which was preventable by an ICD was between 60 and 70% for patients in NYHA class II but fell to between 25 and 40% for patients in NYHA class III. This is higher than the proportion of SCD

in the subgroup of patients in PROVE-HF who had an LVEF of 35% or less(73). In this subgroup, 23% of deaths were due to SCD(73). Unfortunately, the subgroup analysis by LVEF did not report NYHA class(73). However, based on reported NYHA class of the whole study population and the relative size of this subgroup (82% of the total population), at least 64% of patients in the subgroup with an LVEF of 35% or less had NYHA class II symptoms at baseline(72, 73).

As discussed in section 1.5.3, appropriate ICD therapy does not necessarily equal a life saved. In MADIT II, the proportion of patients receiving a shock at 12 months was greater than 15%(36). However, a later analysis of the MADIT II data reported an absolute risk reduction in mortality between the ICD group compared to the medical therapy group of only 1% (+/-4) at 12 months(70). This may be explained to some extent by the ICD programming in MADIT II, which was left to the discretion of the treating physician(36). Later trials comparing different ICD programming strategies identified several strategies to reduce shock rates, through improved discrimination algorithms, using discrimination algorithms at faster heart rates (high-rate group) and increasing the number of intervals of detection prior to delivering therapy (delayed therapy group)(26, 27). In MADIT-RIT, 27% of patients received appropriate ICD therapy in the conventional programming group, compared to 13% of patients in the high-rate group and 8% in the delayed therapy group(26). This difference was driven by a reduction in appropriate ATP in the two experimental groups, rather than a reduction in appropriate shocks(26). The mean follow-up duration was 1.4 years, over which period mortality rates were significantly lower in the high-rate and delayed therapy groups compared to the conventional programming group(26). In PROVIDE, conventional programming was used in the control group compared to a combined strategy of delayed therapy, more aggressive discrimination algorithms and ATP at higher rates in the experimental group.(27). The proportion of patients receiving a shock in the experimental group was 7.2% at 12 months, compared to 12.2% of patients in the conventional group(27). The proportion of patients receiving ATP was also lower in the experimental group compared to the control group, though this difference was driven by reduced inappropriate (as opposed to appropriate) ATP in the experimental group(27). As with MADIT-RIT, mortality was lower in the experimental group(27). The lower mortality amongst patients that received lower rates of ICD therapies (ATP or shocks) suggest that,

with conventional programming, many patients may receive therapy for ventricular arrhythmias that would have resolved spontaneously if left untreated. Therefore, appropriate ICD therapy does not necessarily equal a life saved and we may overestimate the impact of ICDs if we only consider rates of appropriate therapy without the context of how the devices were programmed. Of the studies in this review that report on ICD therapy only one mentions ICD programming strategies, stating that programming strategies using higher rates and delayed detection were encouraged(112). However, programming was still at the discretion of the treating physician and the actual programming strategies that were used were not reported(112).

4.5 Impact on policy and practice

This review highlights that a large proportion of patients with HFrEF have delayed LV remodelling if they are treated with OMT (which includes sacubitril/valsartan) for longer than three months. Furthermore, a large proportion of these patients with HFrEF have an improvement in their LVEF such that they would no longer be considered eligible for a primary prevention ICD.

The included population all had HFrEF at baseline as defined by an LVEF of 35% or less, which was persistent despite at least three months of OMT (including ACE inhibitor or ARB, as tolerated). As discussed in section 1.4.3, persistent LVEF of 35% or less despite three months of OMT is an indication for a primary prevention ICD according to current ESC and NICE guidelines(3, 12). In this group of patients, as little as three months of sacubitril/valsartan was sufficient for some patients to demonstrate LV remodelling to the extent that they would no longer be considered eligible for a primary prevention ICD. By six months of sacubitril/valsartan, between 39 and 40% of patients were no longer eligible for a primary prevention ICD, predominantly due to improvements in their LVEF. This means that up to 40% patients with HFrEF may no longer be considered eligible for a primary prevention ICD if reassessment of LV function were delayed until patients have been on OMT for longer.

However, delaying ICD implantation may result in higher mortality. Patients remain at

higher risk of ventricular arrhythmias prior to LV remodelling, which could result in higher rates of SCD if ICD implantation was delayed. As discussed in section 4.2.2, estimating this risk from the studies included in this review is not possible, as no studies reported SCD separately from all-cause mortality. Three studies reported the proportions of patients with ICDs (or CRT-Ds) who experienced appropriate therapy from their device for VT or VF. However, two of these studies included variable proportions of patients with a *secondary* prevention ICD and patients with secondary prevention ICDs are at higher risk of ventricular arrhythmias compared to patients with primary prevention ICDs(112, 138, 147).

4.5.1 Impact of potential changes to OMT guidelines

In future, guidelines for initiating and up-titrating OMT may change. This could limit the applicability of this review, as patients in the included studies were treated according to contemporaneous guidelines. Registry data highlights that initiation and up-titration of heart failure medications is often slow(144). EVOLUTION-HF found that one year after patients were commenced on prognostically important medications for HFrEF the proportions that attained prescription of maximum doses was low, ranging from 5% for MRA and 28% for ARNI(144). This means that patients may be on medication for heart failure for a long time before they are deemed to be on 'optimal' doses. The implications of this are unclear. Novel pathways of rapid up-titration of OMT have been tested(170, 171), which may impact on the total time patients have been on heart failure medication by the time they reach three months of OMT. It is unclear whether this would impact on this review's key findings.

Some authors have argued against our current stepwise up-titration approach, arguing that the benefit of such an approach is unfounded(172, 173). Current guidelines assume that patients in key clinical trials were on optimal doses of medication(172). However, this is often not true. In MERIT, a key trial of beta-blockers in patients with HFrEF, only 64% of patients were prescribed the target drug doses(174). Similarly in EMPHASIS, a key trial of MRAs in patients with HFrEF, only 60% of patients were prescribed the target dose(71). Nevertheless, the benefits of higher doses of OMT have been shown in other trials, albeit to modest degrees(15, 175). Additionally, clinical guidelines recommend adding new heart

failure medications in a stepwise fashion with the order of drugs introductions largely determined by the year in which each drug was licensed(173). However, few drug sequencing trials have been conducted and as such the current recommendations may not be the best way to maximise the positive effects of these medications(173). CIBISS III is one of the few sequencing trials. It showed no difference in all-cause mortality or heart failure hospitalisation between starting a beta-blocker or ACE inhibitor first(176). Several authors have made their own recommendations about drug sequencing in an attempt to minimise intolerance to prognostically significant medication(17, 173).

If alternative sequencing is adopted, this could have implications for the applicability of the current review, particularly if there is a move towards prescription of ARNI upfront, rather than reserving this for patients whose LV function does not sufficiently improve on either an ACE inhibitor or ARB. Indeed, a recent network meta-analysis found a trend towards lower mortality in patients prescribed OMT combinations including an ARNI compared to ACE inhibitors or ARBs, though this was not statistically significant(177). However, ARNI first line is currently only a IIb indication in the ESC guidelines(3). IIb recommendations are made where the evidence for a particular approach is less well established and mean that the intervention "may be considered"(3).

4.6 Future research

4.6.1 Individual participant data analysis

One way of improving confidence in the effect sizes reported in this review would be to incorporate an analysis based on individual participant data, rather than just the aggregate data available in the published manuscripts. Using individual participant data would enable verification of the results in the original studies(178). It would also overcome the issue of overlapping participants in different studies (see section 3.1.2) as duplicate data could be removed prior to analysis(178).

Analysing individual participant data would additionally enable the review's primary outcome (change in complex device eligibility) to be reported for a greater number of studies. From the aggregate data that is published and included in this review, only three studies reported this outcome (see section 3.3.1)(113, 136, 137). However, all 14 studies

reported follow-up LVEF assessments, which is the main determinant of ICD eligibility(112, 113, 127-138). Analysis of individual participant data would permit this binary LVEF outcome to be calculated for all studies and incorporated into the analysis. This would increase confidence in the effect size. Furthermore, there would be increased granularity of data for the pre-specified subgroups (see section 3.5)(178). Outcomes for patients with or without CRT and for patients with different heart failure aetiologies could be analysed for a greater number of studies than was possible based on aggregate data, which would improve confidence in the effect size and provide useful extra information on these distinct cohorts.

An analysis of individual participant data would also allow additional studies to be included in the review. One example is the PROVE-HF study(72). PROVE-HF was excluded from the review because, at baseline, not all patients were prescribed OMT and some patients had an LVEF of more than 35%(72). However, many patients in this study may have met the review's eligibility criteria. If individual patient data was available, individual patients who met the eligibility criteria could be included. This would increase the total number of patients in the review, which would increase confidence in the results.

There are disadvantages to individual participant data analyses. Firstly, it is resource intensive both for the review team and the original study authors(178). For this review, it is likely that a large number of authors would need to be contacted as it is likely that a large number of studies have included some eligible patients. For example, 102 studies were excluded because they used LVEF of 40% or less as one of their inclusion criteria and did not report separately on the subgroup of patients with an LVEF of 35% or less (see section 3.1.1). It is likely that most (if not all) of these 102 studies will have included some patients with an LVEF of 35% or less at baseline that would be eligible for inclusion in this review if individual participant data was available. Given the large numbers of studies involved, it is highly likely that information would not be available for all studies, either because data has not been stored or because study authors do not respond to requests for data(178). Study authors not responding would be a particular concern given the lack of response from the majority of authors that were contacted as part of the current review, which may introduce reporting bias.

4.6.2 Future randomised control trials

All of the studies included in this review were observational, with attendant risk of bias (see section 4.2). This affects confidence in the reported proportion of patients in whom the LV function improved to an LVEF of greater than 35%. An RCT to compare a delayed ICD implantation strategy to usual care would help address this question. Furthermore, there are uncertainties in the potential rates of SCD if ICD implantation were delayed, which an RCT could help to answer. There is one ongoing RCT that may reduce uncertainties regarding the potential rates of SCD. BRITISH(179) is a trial of patients with HFrEF secondary to non-ischaemic cardiomyopathy who have late gadolinium enhancement suggesting myocardial scar on cardiac MRI. Inclusion criteria for the trial include prescription of OMT for at least three months. Participants are being randomised to either an ICD (or CRT-D if they meet standard CRT indications) or an implantable loop recorder (or CRT-P if they meet standard CRT indications)(179). The primary outcome is all-cause mortality, with SCD as a key secondary outcome(179). It started recruiting in 2023. This trial will provide data regarding the rates of both mortality and ventricular arrhythmias in a population with HFrEF who are prescribed OMT according to current guidelines. Whilst this trial is only recruiting a selected group of patients with HFrEF, it may still provide useful data regarding SCD rates for planning an RCT into delayed remodelling.

If uncertainties regarding the risk of SCD remain, or if the risk of SCD remains unacceptably high, wearable ICDs could be tested as part of an RCT, as this would reduce risk of SCD in patients that were randomised to delayed ICD implantation. Wearable ICDs are commercially available devices, consisting of an external defibrillator incorporated into a vest(180). They can detect ventricular arrhythmias and deliver shocks(180). They currently have a IIb recommendation in ESC guidelines for use as a bridge to an ICD(3). However, the risk of SCD must be offset against both the risks of the device (see section 1.4.1) and potential futility (e.g., if a patient's LV function improves before the need for any appropriate ICD therapy).

A future RCT would also provide contemporary data for an up dated cost-effectiveness analysis of primary prevention ICDs in patients with HFrEF. As discussed in section 1.4.4, the current NICE guidelines are based on a health economic calculations using data prior to

2012(12, 57). Based on these calculations, the cost per QALY for a primary prevention device is close to £30,000 for some patient groups already(12). If the reported effect size in this review is accurate, this would make ICDs significantly more expensive per QALY, which could alter future funding recommendations.

4.7 Conclusion

This review summarises the existing evidence for delayed left ventricular remodelling in patients with HFrEF, as defined as an LVEF of 35% or less despite at least three months of OMT. In this group, a large proportion of patients showed an improvement in their LVEF to greater than 35% following a further six to 24 months of OMT. This improvement in LVEF means that if decision-making for complex device implantation was delayed until patients with HFrEF had been on OMT for longer than three months, many patients would no longer be considered eligible for a primary prevention ICD according to current ESC and NICE guidelines(8). This suggests many patients with HFrEF could potentially avoid primary prevention ICD implantation.

However, the safety of any strategy to delay ICD implantation is not clear from this review. Whilst six of the included studies reported mortality, none of the studies reported SCD distinct from all-cause mortality. Three studies reported either ICD shock rates or frequency of ventricular arrhythmias, which could be used as a surrogate marker for SCD. However, only one of these studies was explicitly in a primary prevention population, none of these three studies specified the ICD programming strategies used and all included patients on amiodarone. As such, it is difficult to draw conclusions regarding the risk of delaying primary prevention ICD implantation from these studies.

In the future, it may be possible to implant fewer primary prevention ICDs by delaying decision-making until patients with HFrEF have been on OMT for longer. This could be of benefit both to individual patients and the wider health service. However, this will only be possible if it can be done safely. As such, future research should focus on addressing the gaps in knowledge highlighted in this review regarding the risk of SCD in patients with HFrEF prescribed contemporary OMT.

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Appendices

Appendix 1 - search strategy

Search strategy for MEDLINE (Ovid). Rows combined with 'OR' (or 'NOT' if specified), columns combined with 'AND'

Population terms	Intervention terms	Outcome terms	Study terms
heart failure, systolic/	Angiotensin-Converting Enzyme Inhibitors/	ventricular remodeling/	randomized controlled trial.pt.
ventricular function, left/	Angiotensin Receptor Antagonists/	ventricular remodel?ing.mp.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
ventricular dysfunction, left/	Neprilysin/	(delayed OR late OR reverse) ADJ2 remodel?ing.mp.	(retraction of publication or retracted publication).pt.
ventricular function.mp.	sacubitril adj2 valsartan.mp.	ejection fraction.mp.	(animals not humans).sh. – 'NOT'
ventricular dysfunction.mp.	entresto.mp.		((comment or editorial or meta-analysis or practice-guideline or review or letter) not "randomized controlled trial").pt. – 'NOT'
cardiomyopath*.mp.	LCZ?696.mp.		(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt. – 'NOT'
	angiotensin-converting enzyme inhibitor*.mp.		exp Cohort Studies/
	angiotensin receptor antagonist*.mp.		cohort$.tw.
	Heart Failure, systolic/dt, th [Drug Therapy, Therapy]		controlled clinical trial.pt.
			Epidemiologic Methods/
			exp Case-Control Studies/
			(case$ and control$).tw.

Search strategy for EMBASE (Ovid). Rows combined with 'OR' (or 'NOT' if specified), columns combined with 'AND'

Population terms	Intervention terms	Outcome terms	Study terms
systolic heart failure/	dipeptidyl carboxypeptidase inhibitor/	heart ventricle remodeling/	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
heart left ventricle function/	Angiotensin Receptor Antagonist/	ventricular remodel?ing.mp.	retracted article/
heart left ventricle failure/	membrane metalloendopeptidase/	(delayed OR late OR reverse) ADJ2 remodel?ing.mp.	(animal$ not human$).sh,hw. – 'NOT'
ventricular function.mp.	sacubitril-valsartan.mp.	ejection fraction.mp.	(book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ – 'NOT'
ventricular dysfunction.mp.	entresto.mp.		(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ – 'NOT'
cardiomyopath*.mp.	LCZ?696.mp.		exp cohort analysis/
	angiotensin-converting enzyme inhibitor*.mp.		exp longitudinal study/
	angiotensin receptor antagonist*.mp.		exp prospective study/
			exp follow up/
	systolic heart failure/dt, th [Drug Therapy, Therapy]		cohort$.tw.
			exp case control study/
			(case$ and control$).tw.

Search strategy for CINAHL Ultimate (EBSCO). Rows combined with 'OR', columns combined with 'AND'

Population terms	Intervention terms	Outcome terms	Study terms
(MH "Ventricular Dysfunction, Left")	(MH "Angiotensin-Converting Enzyme Inhibitors")	(MH "Ventricular Remodeling")	(MH "Case Control Studies+") OR (MH "Prospective Studies+")
(MH "Ventricular Function, Left")	(MH "Angiotensin II Type I Receptor Blockers")	TX (ventricular remodel?ing)	cohort or case control or longitudinal or observational or cross sectional or
TX (ventricular function)	TX (sacubitril)	TX (delayed remodel?ing)	(MH "Clinical Trials+")
TX (ventricular dysfunction)	TX (sacubitril-valsartan)	TX (late remodel?ing)	randomised control trial or randomised controlled trial or rct or randomized control trial or randomized controlled trial
TX (cardiomyopath*)	TX (entresto)	TX (reverse remodel?ing)	
	TX (LCZ?696)	TX (ejection fraction)	
	TX (angiotensin-converting enzyme inhibitor*)		
	TX (angiotensin receptor antagonist*)		

Search strategy for Cochrane Trials and Cochrane Database of systematic reviews. Rows combined with 'OR', columns combined with 'AND'

Population terms	Intervention terms	Outcome terms	Study terms
heart failure, systolic/	Angiotensin-Converting Enzyme Inhibitors/	ventricular remodeling/	randomized controlled trial
ventricular function, left/	Angiotensin Receptor Antagonists/	ventricular remodel?ing.mp.	(random$ or placebo$ or single blind$ or double blind$ or triple blind$)
ventricular dysfunction, left/	Neprilysin/	(delayed OR late OR reverse) ADJ2 remodel?ing.mp.	(retraction of publication or retracted publication)
ventricular function.mp.	sacubitril.mp.	ejection fraction.mp.	exp Cohort Studies
ventricular dysfunction.mp.	sacubitril-valsartan.mp.		cohort$
cardiomyopath*.mp.	entresto.mp.		controlled clinical trial
	LCZ?696.mp.		Epidemiologic Methods
	angiotensin-converting enzyme inhibitor*.mp.		exp Case-Control Studies
	angiotensin receptor antagonist*.mp.		(case$ and control$)
	Heart Failure, systolic/dt, th [Drug Therapy, Therapy]		

Search strategy for Web of Science. Columns combined with 'AND'

((((ALL=(left ventricular dysfunction)) OR ALL=(heart failure with reduced ejection fraction)) OR ALL=(ventricular dysfunction)) AND (((ALL=(ventricular remodel?ing)) OR ALL=(ejection fraction)) AND ((((ALL=(entresto)) OR ALL=(sacubitril valsartan)) OR ALL=(angiotensin receptor antagonist)) OR ALL=(angiotensin-converting enzyme inhibitor))))	(((ALL=(randomized controlled trial)) OR ALL=((random$ or placebo$ or single blind$ or double blind$ or triple blind$))) OR ALL=(cohort$)) OR ALL=((case$ and control$))

Appendix 2 - PROSPERO proforma

PROSPERO
International prospective register of systematic reviews

1. * Review title.

Delayed left ventricular reverse remodelling in patients with heart failure and reduced ejection fraction treated with optimal medical therapy

2. Original language title.

n/a

3. * Anticipated or actual start date.

15/05/2023

4. * Anticipated completion date.

30/11/2023

5. * Stage of review at time of this submission.

The review has not yet started: Yes

6. * Named contact.

Laurence Whittaker

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Whittaker

7. * Named contact email.

laurence.whittaker@nhs.net

8. Named contact address

Department of Cardiology, James Cook University Hospital, Middlesbrough

9. Named contact phone number.

10. * Organisational affiliation of the review.

Academic Cardiovascular Unit, South Tees Hospitals NHS Foundation Trust

11. * Review team members and their organisational affiliations.

Dr Laurence Whittaker. Academic Cardiovascular Unit, South Tees Hospitals NHS Foundation Trust and Hull York Medical School
Dr Vivesh Jeyalan. Academic Cardiovascular Unit, South Tees Hospitals NHS Foundation Trust
Dr Chris Wilkinson. Academic Cardiovascular Unit, South Tees Hospitals NHS Foundation Trust and Hull York Medical School

Dr Matthew Dewhurst. North Tees and Hartlepool NHS Foundation Trust
Dr Michael Chapman. South Tees Hospitals NHS Foundation Trust
Dr Noortje Uphoff. Centre for Reviews and Dissemination, University of York

12. * Funding sources/sponsors.

LW was funded by South Tees NHS Foundation Trust

13. * Conflicts of interest.

CW has received research funding from Bristol-Myers Squibb

14. Collaborators.

Professor Nick Linker. Academic Cardiovascular Unit, South Tees Hospitals NHS Foundation Trust

15. * Review question.

How does prolonged (more than 3 months) optimal medical therapy (OMT) for heart failure with reduced ejection fraction (HFrEF) impact on left ventricular (LV) reverse remodelling?

In HFrEF, current European and UK guidelines recommend reassessing LV function after 3 months of OMT to decide whether or not to offer an implantable cardiovertor-defibrillator (ICD), with implants only recommended if the LV ejection fraction remains less than or equal to 35%. In practice, this 3 month time-point is also used to decide whether or not to offer a cardiac resynchronisation pacemaker or defibrillator (CRT-P, CRT-D). These devices (ICD, CRT-P and CRT-D) are expensive and come with risks. Implant risks include 1% risk of bleeding, 1% risk of infection, 1% risk of pneumothorax and 4-5% risk of lead displacement, the latter of which would necessitate a further procedure for lead repositioning. For the devices with a defibrillator function (ICD and CRT-D) there is also a 1-2% risk each year of an 'inappropriate' shock, meaning a shock delivered due to either device malfunction or misidentification of a non life-threatening heart rhythm. Additionally, there is emerging data that some patients may undergo 'delayed' reverse remodelling, beyond 3 months of OMT to the point that the ejection fraction is greater than 35%. This would mean they would no longer be candidates for an implantable device. Current systematic reviews in this area are either restricted to assessing a single component of OMT (the drug Sacubitril/Valsartan) and/or do not represent contemporary OMT.

16. * Searches.

Searches include: Ovid MEDLINE, EMBASE, CINAHL, Cochrane Trials and Cochrane Database of systematic reviews, and Web of Science from 01/01/2014 to 12/04/2023. Relevant reviews will be tagged during screening and their reference lists checked="checked" value="1" for relevant studies which have been missed.

The date restriction is to reflect current optimal medical therapy, which includes the use (if appropriate for the individual patient) of Sacubitril/Valsartan.

Only studies published in English will be included in the final analysis. However, relevant studies not published in English will be included in the search and the numbers excluded from further analysis based on language will be recorded.

The search strategy was devised in collaboration with a specialist librarian at Hull York Medical School.

17. URL to search strategy.

18. * Condition or domain being studied.

Heart failure with reduced ejection fraction (HFrEF).

Heart failure is a clinical syndrome defined by the presence of key symptoms (e.g. breathlessness and fatigue) with or without clinical signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema). HFrEF is a subgroup of heart failure caused by reduced left ventricular systolic function.

European and UK guidelines define HFrEF by left ventricular ejection fraction (LVEF) of less than or equal to 35%.

19 Participants/population.

Participants must be aged 18 or over

Inclusions:

Heart failure with reduced ejection fraction(HFrEF) despite at least 3 months of optimal medical therapy (OMT) (HFrEF defined as left ventricular ejection fraction 35% or less measured by TTE, TOE, MRI or nuclear, but same imaging modality must be used for all patients/timepoints within each study)

Exclusions:

Already treated with OMT (which includes sacubitril/valsartan) for 12 months or more

Cardiac resynchronisation therapy (CRT) device implanted in 3 months prior to the baseline assessment of left ventricular ejection fraction or are planned to undergo CRT implant during the course of the study.

Acute coronary syndrome (ACS) (or coronary revascularisation), or had an ablation procedure for atrial fibrillation or premature ventricular complexes in 3 months prior to the baseline assessment of left ventricular ejection fraction

Untreated severe primary valvular heart disease

Reversible cause of HFrEF, including tachycardia-induced cardiomyopathy, takotsubo cardiomyopathy or peripartum cardiomyopathy

Aetiology of HFrEF that typically progresses despite treatment, such as chagas cardiomyopathy

HFrEF secondary to chemotherapy unless the last dose of chemotherapy was given more than 12 months prior to the baseline LVEF assessment

Complex congenital heart disease

Studies which include subgroups which meet the inclusion/exclusion criteria will be included provided the target subgroup data is presented separately.

20. * Intervention(s), exposure(s).

The intervention of interest is prolonged (more than 3 months) optimal medical therapy (OMT) for HFrEF.

Current OMT is a combination of four classes of drugs (if tolerated), titrated to the highest tolerated doses.

The classes are beta-blockers, mineralocorticoid receptor antagonists (MRA), renin-angiotensin system antagonists (including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and combination angiotensin receptor blocker/neprilysin inhibitor (ARNI)), and sodium-glucose co-transporter 2 inhibitors (SGLT2i).

The search will be restricted to studies after 2014 as this was the year when the pivotal ARNI trial, PARADIGM-HF, was published, which demonstrated their benefit over ACEi/ARBs. Following PARADIGM-HF, ARNIs were quickly adopted into clinical practice and guidelines. Preliminary searches have identified several studies demonstrating left ventricular remodelling with ARNI. However, our review is designed to be pragmatic. ARNI are not universally tolerated and patients who do not tolerate ARNI will continue to be treated with ACEi/ARBs. As such, we will include recent studies (since 2014) which include patients treated with ACEi/ARBs.

It is anticipated that few studies will include patients treated with the fourth class, SGLT2i, as they were licensed for HFrEF in 2020. However, since SGLTi are not known to impact on LVEF this should not present a major limitation.

21. * Comparator(s)/control.

Short duration (3 months) of optimal medical therapy (OMT) for heart failure. However, data from patients who have already had significant left ventricular remodelling such that their ejection fraction is more than 35% after less than or equal to 3 months of OMT will not be included

22. * Types of study to be included.

Randomised-control trials, cohort studies and case-control studies will be included.

Reviews, case reports, case series, abstracts and conference proceedings will be excluded.

Studies not published in English will be recorded, but not included in further analysis.

23. Context.

There will be no restrictions based on context. Studies in inpatient, outpatient, home or institutional settings will be included

24. * Main outcome(s).

Proportion of patients who positively remodel such that their left ventricular ejection fraction is more than 35%

Proportion of patients with significant positive remodelling (improvement in left ventricular ejection fraction more than/equal to 5%)

Measures of effect

Risk ratio with 95% confidence intervals

25. * Additional outcome(s).

1. Mean change in left ventricular ejection fraction

2. Mortality

3. Heart failure hospitalisation

4. Implantable Cardiovertor-Defibrillator (ICD) therapy - anti-tachycardia pacing (ATP), shocks (both appropriate and inappropriate)

5. Change in New York Heart Association (NYHA) class

6. Heart failure medications - proportion of patients (and percentage of maximum dose)on each of angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor II blocker (ARB), angiotensin receptor II blocker/neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid receptor antagonist (MRA), Sodium-glucose co-transporter 2 inhibitor (SGLT2i) at baseline and end of follow-up

Measures of effect

Risk ratio with 95% confidence intervals for binary outcomes. Mean difference with standard deviation for continuous outcomes.

26. * Data extraction (selection and coding).

Stage 1: All abstracts will be screened by two reviewers independently. Disagreement will be resolved by consensus or, if consensus is not reached, by consultation with a third reviewer

Stage 2. Full texts included at stage one will similarly reviewed independently by two reviewers.

Disagreement will be resolved by consensus or, if consensus is not reached, by consultation with a third reviewer. Reasons for exclusion will be recorded.

Stage 3. Data will be extracted by one reviewer and a random sample of 10% will be checked by a second reviewer. Disagreement will be resolved by consensus or, if consensus is not reached, by consultation with a third reviewer

Covidence will be used for screening and data extraction. A data extraction form will be created and piloted with 2 studies. Data extracted will include general information (title, first author's name, publication year, study location), study characteristics (study type, start and end dates, funding sources, possible conflicts of interest for study authors), participant information (inclusion/exclusion criteria, recruitment method, sample size, age, gender), baseline data (medications/doses/durations, LVEF, NYHA class, ICD/CRT) and outcome data (change in medications/doses/durations, LVEF, NYHA class, ICD therapy, mortality, heart failure hospitalisation).

27. * Risk of bias (quality) assessment.

The Newcastle-Ottawa scale will be used for non-randomised studies and the Cochrane Risk of Bias 2 tool will be used for randomised-control trials to assess for risk of bias for each full text included after stage 2 review. Assessments will be performed by a single reviewer and checked by a second reviewer. Disagreement will be resolved by consensus or, if consensus is not reached, by consultation with a third reviewer.

Studies will be included in the synthesis regardless of risk of bias, but this will be reported for each study.

Risk of bias assessments will inform our confidence in the results, which will be reflected in the conclusions and implications for practice sections of the review.

28. Stategy for data synthesis.

We will start with a descriptive summary of the studies. Data on participant numbers/demographics/characteristics, intervention, study characteristics, and primary and secondary outcomes will be tabulated. Risk of bias will also be described.

It is likely that this will be a narrative synthesis; it is anticipated that there will be substantial

heterogeneity between populations and methodologies such that meta-analysis is not possible. Data will be synthesised according to the main and additional outcomes. Consideration will be given to moderator variables, at a study level (quality, design, setting) and around sample characteristics (e.g. age, heart failure aetiology, baseline ejection fraction, baseline NYHA class). There will be a critical discussion of methodology and evidence used (quality, validity, generalisability) with an emphasis on possible sources of bias.

It is anticipated that results will be amenable to description by duration of OMT (e.g. 3-6 months, 6-9 months, 9-12 months, more than 12 months) and/or category of baseline medical therapy (ACEi/ARB or ARNI) - e.g:

1. Baseline treatment with more than or equal to 3 months of either ACEi or ARB and treatment with starting ARNI

2. Baseline treatment with 3 months of ARNI and treatment with continuing ARNI

3. Baseline treatment with 3 months of ACEi or ARB and treatment with continuing ACEi or ARB

Depending on the results, subgroup analysis by aetiology of heart failure (ischaemic vs non-ischaemic) and presence/absence of CRT may also be possible.

If studies are sufficiently comparable then meta-analysis will be considered, most likely using a random effects model in consultation with a statistician.

29. * Analysis of subgroups or subsets.

None planned.

30. * Type and method of review.

Type of review

Systematic review

Health area of the review

Cardiovascular

31. Language.

English

32. * Country.

England

33. Other registration details.

34. Reference and/or URL for published protocol.

35. Dissemination plans.

The review will be submitted for peer-review publication and presentation at a national or international cardiology conference

36. Keywords.

heart failure, ventricular remodelling, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Antagonists, sacubitril-valsartan

37. Details of any existing review of the same topic by the same authors.

38. * Current review status.

39. Any additional information.

40. Details of final report/publication(s) or preprints if available.

Appendix 3 - Newcastle-Ottawa Scale proforma for cohort studies(116)

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative ***(one star)***
   b) Somewhat representative ***(one star)***
   c) Selected group
   d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort *(not included in this review – all single cohort studies)*
   a) Drawn from the same community as the exposed cohort ***(one star)***
   b) Drawn from a different source
   c) No description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) Secure record (e.g., surgical record) ***(one star)***
   b) Structured interview ***(one star)***
   c) Written self report
   d) No description
   e) Other

4) Demonstration that outcome of interest was not present at start of study
   a) Yes ***(one star)***
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders *(not included in this review – all single cohort studies)*
   a) The study controls for age, sex and marital status ***(one star)***
   b) Study controls for other factors (list) _____ ***(one star)***
   c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
   a) Independent blind assessment ***(one star)***
   b) Record linkage ***(one star)***
   c) Self report
   d) No description
   e) Other

2) Was follow-up long enough for outcomes to occur
   a) Yes ***(one star)***

b) No
Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts
a) Complete follow up- all subject accounted for ***(one star)***
b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***
c) Follow up rate less than 80% and no description of those lost
d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor): *(summary scores not included in this review – see section 2.4)*

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

List of abbreviations

ACE inhibitor - angiotensin converting enzyme inhibitor

ACS - acute coronary syndrome

AF - atrial fibrillation

ARR - absolute risk reduction

ATP - anti-tachycardia pacing

ARB - angiotensin receptor blocker

ARNI - angiotensin receptor blocker/neprilysin inhibitor

BSE - British Society of Echocardiography

CPET - cardiopulmonary exercise test

CRD - Centre for Reviews and Dissemination

CRT - cardiac resynchronisation therapy

CRT-D - cardiac resynchronisation therapy-defibrillator

CRT-P - cardiac resynchronisation therapy-pacemaker

ECG - electrocardiogram

eGFR - estimated glomerular filtration rate

ESC - European Society of Cardiology

ESRC - Economic and Social Research Council

EF - ejection fraction

HF - heart failure

HFpEF - heart failure with preserved ejection fraction

HFrEF - heart failure with reduced ejection fraction

ICD - implantable cardioverter-defibrillator

IHD - ischaemic heart disease

IQR - interquartile range

LBBB - left bundle branch block

LV - left ventricle/left ventricular

LVEF - left ventricular ejection fraction

LVEDV - left ventricular end diastolic volume

LVESD - left ventricular end systolic dimension

LVESV - left ventricular end systolic volume

LVSD - left ventricular systolic dysfunction

MR - mitral regurgitation

MRA - mineralocorticoid receptor antagonist

MRI - magnetic resonance imaging

NHFA - Nation Heart Failure Audit

NICE - National Institute for Health and Care Excellence

NICOR - National Institute for Cardiovascular Outcomes Research

NOS - Newcastle-Ottawa Scale

NT-proBNP - N-terminal pro-brain natriuretic peptide

NYHA - New York Heart Association

PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

OMT - optimal medical therapy

QALY - quality-adjusted life years

RAS - renin-angiotensin system

RCT - randomised control trial

TOE - transoesophageal echocardiogram/echocardiography

TTE - transthoracic echocardiogram/echocardiography

SCD - sudden cardiac death

SD - standard deviation

SGLT2 inhibitor - sodium-glucose co-transporter 2 inhibitor

UK - United Kingdom

VF - ventricular fibrillation

VT - ventricular tachycardia