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REVIEW

# Long-Term Pharmacological Management of Reduced Ejection Fraction Following Acute Myocardial Infarction: Current Status and Future Prospects

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**Abstract:** Heart failure (HF) with reduced ejection fraction is common following acute myocardial infarction (MI), and active medical management can have a profound impact on prognosis. Reviewing relevant clinical trials, we focus on the pharmacological management of left ventricular systolic dysfunction (LVSD) following an acute MI, although there is overlap with the pharmacological management of chronic HF due to reduced ejection fraction. Angiotensin converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists are the mainstay of medical management in patients with LVSD post MI; there may also be a role for anticoagulation. Sacubitril-valsartan (angiotensin receptor neprilysin inhibitor) has not yet been shown to be superior to an ACE inhibitor in reducing cardiovascular mortality and HF events in patients with LVSD post MI. Large randomised trials evaluating sodium glucose transporter 2 (SGLT-2) inhibitors in LVSD post MI are ongoing.

**Keywords:** heart failure, HeFREF, myocardial infarction

## Introduction

Heart failure (HF) is a common complication following an acute myocardial infarction (MI) and may develop early (post MI) or late (chronic HF).[1] Perhaps as many as 40% of patients with a first myocardial infarct develop significant left ventricular systolic dysfunction (LVSD).[2] As the management of acute myocardial ischaemia continues to improve, particularly with the emphasis on early revascularization, so the number of people with significant LVSD following MI will continue to increase. Imaging (typically with echocardiography, but increasingly with magnetic resonance imaging) readily identifies patients with significant left ventricular systolic impairment following an event: active medical management at this point can have a profound impact on the long-term outcome of such patients.

There is considerable overlap between the medications used in patients post MI and those used in the management of chronic HF due to reduced left ventricular ejection fraction (HeFREF). We will focus primarily on the pharmacological management of LVSD post MI.

## Standard Therapy for Post MI LVSD

The medications for secondary prevention following acute MI are well-established.[3] Angiotensin converting enzyme (ACE) inhibitors should be started as soon as a patient is haemodynamically stable Beta-blockers should also be started as soon as possible, but care should be taken in patients with overt HF or at high risk for

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cardiogenic shock. Dual antiplatelet therapy (aspirin and clopidogrel/ticagrelor) should be continued for 12 months (with aspirin alone thereafter). For patients with LVSD post MI, mineralocorticoid receptor antagonists (MRAs) should be started within 3–14 days. We will consider the evidence-base for the therapies shown to be prognostically beneficial in LVSD post MI.

## Beta-Blockers

Beta-blockers have a long history of use following acute MI. Among 54,234 patients included in randomized trials of beta-blockers following acute MI, there was a 23% reduction in the odds of death in long term trials.[4] Timolol was the agent that appeared to have the greatest effect. Noting that the post MI trials were largely conducted in an era when beta-blockers were thought to be contra-indicated in HF, a second analysis from the same group suggested that the beneficial effect of beta-blockers was similar regardless of the presence of HF, but with a suggestion that the absolute benefit was greater amongst patients with HF.[5] The largest single trial of beta-blockers in patients with LVSD post MI (N 1959; all with LV ejection fraction ≤40%) was CAPRICORN:[6] carvedilol conferred a 23% relative risk reduction for mortality with the number needed to treat for one year to save a life of 38 – much the same as the effect of ACE inhibitors in patients with reduced LVEF post MI.[7]

The benefits of beta-blockade in patients with chronic HF due to LVSD are absolutely established and enshrined in all national and international guidelines.[8] Whether beta-blockers are still useful in patients following MI who have normal LV systolic function is not clear. Modern revascularization strategies may mean that they no longer have a role. The first post MI beta-blocker studies for many decades are recruiting patients to study this specific question.[9,10]

## ACE Inhibitors

The second standard therapy used post MI is angiotensin converting enzyme (ACE) inhibitors. Major trials in patients with LVSD post MI have shown that trandolapril,[11] ramipril,[12] and captopril[13] all improve outcomes in patients selected for trial entry on the basis of impaired LV systolic function. The beneficial effect is quite marked: a long-term follow up study from the AIRE investigators suggests that ramipril resulted in life extension of up to 14.5 months.[14]

Lisinopril[15] and captopril[16] also improve outcomes in trials that included all-comers following MI. The effect was smaller in the all-comer studies, presumably reflecting the fact that many patients at low risk of future events were included, suggesting that therapy targeted at those with significant LVSD might be a better strategy than to treat everyone. Table 1 displays the major trials of ACE inhibitors for LVSD post MI.

## Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) are used when ACE inhibitors may not be used, for example, due to intolerance. The OPTIMAAL trial (N 5477) compared losartan and captopril in "high-risk" patients post MI, including patients with HF: there was a non-significant difference in all-cause mortality in favour of captopril, but losartan was better tolerated with fewer discontinuations.[17] In the VALIANT trial (N 14703; patients with HF and 51.8% with imaging evidence of LVSD on enrollment), valsartan was non-inferior to captopril in reducing all-cause mortality in patients with HF post MI.[18]

## Mineralocorticoid Receptor Antagonists

The third member of the trinity of post MI LVSD therapies is the mineralocorticoid receptor antagonist (MRA). Strictly, only eplerenone has been shown to confer benefit post MI: in EPHESUS, 6632 patients with LVSD were recruited 3–14 days post MI. Eplerenone reduced all-cause mortality by 15%.[19] However, of the three agents (beta-blockers, ACE inhibitors and MRAs), MRAs tend to be prescribed in a much smaller proportion of appropriate patients.[20]

## Ivabradine

Ivabradine is the only available $I_f$ inhibitor. It reduces the rate of spontaneous depolarization of the sinus node, thus reducing heart rate with minimal effect on other haemodynamic variables. In the SHIFT trial of 6558 patients with HeFREF,[21] ivabradine reduced the rate of the primary endpoint, cardiovascular death or hospital admission for worsening HF. It had no effect on total mortality. It has an established role in patients with chronic HF for those patients with HeFREF in sinus rhythm with a resting heart rate above 70.

There is a small number of studies of the potential use of ivabradine following MI. None has more than 85 patients. Although a meta-analysis of the available trials[22] found that ivabradine does reduce heart rate and

**Table 1** Trials of ACE Inhibitors Post MI

| Trial | ACEi | N | Female % | Patient Selection | Outcome/Benefit |
|---|---|---|---|---|---|
| ISIS-4[16] | Captopril | 58,050 | 26 | Within 24h of acute MI. All-comers | 0.5/5 week<br>Captopril reduced overall mortality, with the greatest advantage in high-risk patients. |
| GISSI-3[15] | Lisinopril | 19,394 | 22 | Within 24h of acute MI. All-comers | 0.8/6 week<br>Lisinopril reduced overall mortality and the composite outcome of mortality and severe LVSD. |
| SAVE[13] | Captopril | 2,231 | 18 | 3–16 days following acute MI; LVEF ≤40, asymptomatic | 4.2/3.5 years<br>Captopril, in patients with asymptomatic LVSD post MI, reduced over mortality and the morbidity and mortality due to CV events. |
| TRACE[11] | Trandolapril | 1,749 | 28 | 3–7 days following acute MI; LVEF ≤35%, LVSD, or clinical chronic HF | 7.6/3 years<br>Trandolapril, in patients with LVSD post MI, reduced overall mortality, mortality from CV causes, sudden death, and progression to severe HF. |
| AIRE[12] | Ramipril | 2,006 | 26 | 3–10 days following acute MI, clinical evidence of HF | 6/1 year<br>Ramipril, in patients with clinical evidence of HF post MI, reduced overall mortality. |

**Notes:** Studies highlighted in blue recruited "all-comers" with acute myocardial infarction; those in black recruited those with either significantly reduced left ventricular systolic function or those with clinical heart failure. The figures given for outcome are the absolute risk reduction and the median length of follow up.
**Abbreviations:** LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; CV, cardiovascular; HF, heart failure; STEMI, ST-elevation acute MI; AF, atrial fibrillation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

is associated with better left ventricular systolic function and a lower NT-proBNP, only 658 patients were included in total, and it is not possible to draw any firm conclusions. Ivabradine should not be used in preference to up-titration of beta-blockade to target dose.

## Hydralazine/Isosorbide Dinitrate

A trial in just over 1000 African American patients with severely symptomatic HeFREF was stopped early due to a survival advantage for fixed dose hydralazine/isosorbide dinitrate (HISDN) therapy.[23] A meta-analysis suggests that the combination therapy is better than placebo, but less effective than ACE inhibitor.[24] A trial investigating whether it confers benefit in addition to optimal modern therapy is currently recruiting.[25] Whether HISDN has a role specifically following MI is not known.

## Antithrombotic Therapy

Standard advice issued in all guidelines is that patients following acute MI should receive life-long aspirin, with dual antiplatelet therapy used for the first year following any primary percutaneous intervention.[26] Although there is no doubt that patients with atrial fibrillation should be formally anticoagulated with warfarin or a direct oral anticoagulant, the role of anticoagulants in patients in sinus rhythm is less clear.

A meta-analysis of studies using magnetic resonance imaging within a month of an acute ST-segment elevation MI found that 12% of patients with an anterior MI, and nearly 20% of those with an anterior MI and left ventricular ejection fraction below 50%, had an LV thrombus.[27] There may thus be a role for anticoagulants in preventing recurrent events following acute MI, particularly in patients with significant LVSD, in whom the risk of thrombosis is greater.

There is a small group of older studies reporting on the use of warfarin post MI. All showed improvements in outcome with warfarin.[28–30] These studies need to be interpreted with caution given the changes to revascularization strategy and pharmacological therapy that have occurred since they were published. A meta-analysis of the available data in the primary PCI, dual antiplatelet era could only include 873 patients. It reported no benefit from warfarin,[31] but the underlying data are not compelling.

A series of studies using rivaroxaban sheds some light on the issue. In a study of over 15,000 patients with a recent acute coronary syndrome, rivaroxaban (at both low – 2.5 mg twice daily – and high – 5 mg twice daily –

dose) reduced the risk of cardiovascular death, MI, or stroke.[32] In addition, the low dose regimen (only) reduced the risk of all-cause mortality. In stable atherosclerotic disease, the combination of low dose rivaroxaban and aspirin conferred small benefits over aspirin alone (absolute reduction in risk of cardiovascular death, MI or stroke of 1.3%), but at a cost of greater risk of major bleed.[33] The benefits were slightly greater in those patients with underlying coronary artery disease.[34]

In light of these findings, the results of the COMMANDER-HF trial of rivaroxaban at low dose in patients with stable chronic HF due to underlying coronary artery disease were surprising.[35] The low dose, 2.5 mg twice daily, regime shown to be effective following an acute coronary syndrome, was used; the median ejection fraction was 35% and the median NT-proBNP was 2840 $ng.L^{-1}$. However, there was no difference in the rate of the primary endpoint, all-cause mortality, MI or stroke, between rivaroxaban and placebo groups. A subsequent meta-analysis of all the data from studies of patients with HF in sinus rhythm showed no benefit from oral anticoagulant versus placebo.[36]

It does thus seem that there is a possible role for anticoagulation post MI. The only agent with good evidence to support its use is rivaroxaban: studies testing apixaban were neutral and showed a marked increase in the risk of bleeding.[37,38] Patient selection remains difficult: the absolute benefit from anticoagulation is modest and the increased bleeding risk is appreciable. However, patients with significant LV systolic impairment following an acute MI should be offered low dose rivaroxaban therapy.[39]

## Renal Dysfunction

Renal dysfunction is extremely common in patients with significant LVSD. The origin of renal dysfunction is multifactorial: the same disease processes that lead to MI can affect the kidney (vascular disease, hypertension, diabetes); acute MI can lead to reduced renal perfusion; and medical therapy can induce further deterioration in renal function. Renal dysfunction is associated with worse outcome in HF, regardless of clinical setting, from cardiogenic shock post MI[40] to chronic HF.[41]

Renal dysfunction can lead to reluctance to prescribe life-prolonging medication following MI, particularly inhibitors of the renin-angiotensin-aldosterone system.[42] National guidance in the UK, at least, emphasizes the importance of efforts "to initiate, titrate and maintain patients with HeFREF on RAAS inhibitor treatment, whether during intercurrent illness or worsening heart failure".[43]

## Recent Developments in Chronic Heart Failure Management

There have been two major developments in the management of patients with chronic HF due to reduced left ventricular systolic function: the introduction of sacubitril-valsartan and the development of sodium-glucose co-transporter-2 (SGLT-2) inhibitors.

### Sacubitril-Valsartan

Sacubitril-valsartan is now widely used in HeFREF. The PARADIGM-HF study,[44] demonstrated the superiority of the combined angiotensin receptor blocker (valsartan) neprilysin inhibitor (sacubitril) over the only ACE inhibitor shown to improve survival in HF, enalapril. The effect was so striking (20% reduction in the rate of cardiovascular death and 21% reduction in the rate of HF hospitalization; number needed to treat to prevent one of the primary outcomes: 21) that the trial was stopped early. It is important to recognize that the beneficial effect is seen on top of extremely good background management: over 90% of patients were on a beta-blocker, and over 50% were on an MRA.

An array of subsidiary publications from PARADIGM-HF has shown that there are no subgroups of patients who do not benefit from, and no cardiovascular endpoint that is not beneficially affected by, sacubitril-valsartan and it has been incorporated into national and international guidelines very rapidly. Depending upon how rigorously the entry criteria for the PARADIGM-HF trial are applied, at least 60% of patients with HeFREF are suitable for sacubitril-valsartan.[45]

A more recent development has been the publication of the results of the PARAGON trial, which compared sacubitril-valsartan with valsartan alone in patients with HF and normal LVEF.[46] The trial was formally neutral: the primary end-point, the composite of heart failure hospitalizations and cardiovascular death, was numerically less common in the patients treated with sacubitril valsartan, but the result did not reach conventional statistical significance (rate ratio, 0.87; 95% confidence interval, 0.75 to 1.01; P = 0.06).

### SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) is responsible for the active transport of filtered glucose from the urinary space in the proximal convoluted tubule of the nephron.

When an SGLT-2 inhibitor is started, urinary glucose excretion thus increases, with a fall in blood glucose. The glucose remaining in the urine acts as an osmotic diuretic.

The first trial of an SGLT-2 inhibitor powered for cardiovascular endpoints, EMPA-REG, reported that empagliflozin reduces the composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke.[47] The most unexpected result, however, was a marked reduction in HF events, which led to subsequent studies of SGLT-2 inhibitors specifically in patients with HF, regardless of the presence of diabetes.

In DAPA-HF, 4744 patients were randomized to receive dapagliflozin or placebo in addition to standard HF therapy.[48] Dapagliflozin reduced the primary endpoint of worsening HF or cardiovascular death by 30%, and total mortality by 17%. The beneficial effects were seen regardless of the presence of diabetes. As with PARADIGM-HF, the improvements were seen on top of exemplary medical therapy: over 90% were taking a blocker of the renin-angiotensin system; 90%, a beta-blocker; and over 70%, an MRA.

In EMPEROR-Reduced, 3730 patients were randomized to empagliflozin or placebo in addition to standard therapy.[49] Empagliflozin reduced the primary endpoint of cardiovascular death or hospitalization for worsening HF by 25%, again regardless of the presence of diabetes. However, there was no effect on total mortality.

## Comprehensive Management

To try to quantify the possible effect of the novel therapies on outcomes, a cross-trial analysis compared standard therapy (beta-blocker plus ACE inhibitor (or angiotensin receptor blocker) with comprehensive therapy (beta-blocker, MRA, sacubitril valsartan and SGLT-2 inhibitor).[50] Comprehensive therapy improved survival free from hospitalization by 8.3 years for a 55 year old and 2.7 years for an 80 year old, a quite remarkable increase.

## Omecamtiv Mecarbil

Omecamtiv mecarbil has a novel mechanism of action: it is a selective myocardial myosin activator. In GALACTIC-HF,[51] 8256 patients with symptomatic HeFREF were randomized to receive omecamtiv mecarbil or placebo. At a median of 21.8 months, there was a slightly lower incidence of the primary end point (a first heart-failure event or cardiovascular death) in the omecamtiv mecarbil than the placebo group (37 v 39.1%). Although the difference was formally statistically significant (P = 0.03), there was no effect of omecamtiv on cardiovascular death or on symptoms (measured by the Kansas City Cardiomyopathy Questionnaire). It is difficult to predict whether there will be further development of omecamtiv given its very modest effect. Given its mechanism of action (and association with an increase in troponin in early dose-ranging studies), it seems unlikely it will be used soon after MI.

# Recent Developments and Future Prospects in LVSD Post MI

The newer agents shown to be prognostically beneficial in chronic HF may have a role in patients with LVSD post MI. Several studies have been initiated to explore the role of sacubitril-valsartan and SGLT-2 inhibitors.

## Sacubitril-Valsartan

The PARADISE-MI study compared sacubitril-valsartan with ramipril in patients with LVSD following an acute MI (started within 7 days of presentation); the primary endpoint was a composite of cardiovascular mortality and first HF event (first hospitalization or diagnosis in outpatient setting).[52] Patients had to have a low LVEF (≤40%) or clinical evidence of congestion requiring treatment. At least one additional risk factor was required. The results have not yet been formally published but presented at the American College of Cardiology 2021 Scientific Session.[53] Sacubitril-valsartan did not significantly reduce cardiovascular mortality or HF events compared with ramipril. A range of secondary endpoints, particularly the total of HF hospitalization, outpatient HF events, and CV mortality favoured sacubitril valsartan: however, as the primary endpoint was neutral, the secondary endpoints should be taken to be hypothesis-generating only. Table 2 displays the three major trials evaluating sacubitril-valsartan in HF due to reduced ejection fraction (post MI and chronic HF).

The surprising neutral result of PARADISE-MI, together with the neutral effect of sacubitril valsartan in patients with HF and normal ejection fraction in the PARAGON study,[37] have led some commentators to wonder if the marked reduction in mortality reported in PARADIGM were an outlier. However, the PARADISE-MI cohort consisted of patients with LVSD post MI, which does make them different to chronic HF patients studied in

**Table 2** Trials of Sacubitril-Valsartan in Heart Failure (PARASDISE-MI = Post MI Trial)

| Trial | N | Female % | Clinical Scenario | Patient Selection | Primary Endpoint | Outcome |
|---|---|---|---|---|---|---|
| PARADISE-MI | 5669 | 24 | Patients within 7 days of presentation with acute MI, randomised to either sacubitril-valsartan or ramipril | **LVEF ≤40%, or clinical evidence of congestion**; plus one additional risk-enhancing factor (age ≥70 years, eGFR <60 mL/min/1.73 $m^2$, DM, prior MI, AF, LVEF <30%, Killip class ≥III, STEMI without reperfusion) | Composite of CV death, HF hospitalization, and outpatient HF (time-to-first event analysis) | Sacubitril-valsartan was not superior to ramipril. Safety and tolerability of sacubitril-valsartan was comparable to that of ramipril. |
| PARAGON-HF | 4822 | 52 | Patients with HeFNEF, randomised to either sacubitril-valsartan or valsartan | **LVEF ≥45%**; NYHA class II–IV | Composite of CV death and total HF hospitalizations | Sacubitril-valsartan was not superior to valsartan in reducing the composite endpoint of CV death and HF hospitalisations. |
| PARADIGM-HF | 8442 | 21 | Patients with HeFREF, randomised to either sacubitril-valsartan or enalapril | **LVEF ≤40%**; NYHA class II–IV | Composite of CV or HF hospitalization | Sacubitril-valsartan reduced CV mortality and HF hospitalisation compared with enalapril. |

**Notes:** PARADISE-MI (Prospective ARNI vs ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction); PARAGON-HF (Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction); PARADIGM-HF (Angiotensin-neprilysin inhibition versus enalapril in heart failure).
**Abbreviations:** LVEF, left ventricular ejection fraction; MI: myocardial infarction; CV, cardiovascular; HF, heart failure; STEMI, ST-elevation acute MI; AF, atrial fibrillation; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

PARADIGM-HF (despite a similar median LVEF). Background therapy used in post-MI care has improved to the point where mortality is much lower than it was historically, even among the high-risk patients recruited for PARADISE-MI, making it much more difficult to demonstrate further improvements in outcome.

Sacubitril-valsartan had a good safety profile and was well tolerated even though there was no initial run-in period with an ACE inhibitor. Current UK NICE guidelines require patients with chronic HF to be on a "stable" dose of an ACE inhibitor or ARB prior to swapping to sacubitril-valsartan.[54] The safety of sacubitril-valsartan in PARADISE-MI gives more weight to the proposal of skipping the ACE inhibitor step in what is already a complex process of initiation and up-titration of guideline-recommended therapy.

## SGLT-2 Inhibitors

Multi-centre RCTs of SGLT-2 inhibitors in LVSD following an acute MI are ongoing. EMPACT-MI compares the effect of the SGTL-2 inhibitor, empagliflozin, with placebo on hospitalization for HF and mortality in patients following acute MI: the study began in December 2020 and is expected to complete in 2022.[55] Patients have to be recruited within 14 days, and have to be at high risk, defined as having a low LVEF (<45%) or clinical evidence of heart failure.

DAPA-MI is another RCT evaluating the same outcomes of hospitalization for HF or cardiovascular death in patients with acute MI but using the SGTL-2 inhibitor dapagliflozin: the study began in December 2020 and is expected to complete in 2023.[56] Patients have to be recruited with 7 days and have an LVEF below 50%.

The success of SGTL-2 inhibitors in chronic HF (DAPA-HF, EMPA-reduced) means that new trials are eagerly awaited; however, as we have seen with PARADISE-MI and sacubitril-valsartan, drugs that have been shown to be prognostically beneficial in chronic HF might not yield the same benefit in patients with LVSD following acute MI.

## Colchicine

While not an HF therapy, colchicine has also been trialled post MI. Colchicine acts primarily via tubulin disruption and down-regulation of multiple inflammatory pathways. As inflammation promotes the development of

atherosclerotic disease, colchicine might improve cardiovascular outcomes post MI. The COLCOT trial compared colchicine (0.5 mg once daily) with placebo (within 30 days of an acute MI): there was a statistically significant reduction in the composite primary endpoint of ischaemic cardiovascular events, predominantly driven by a reduction in urgent hospitalization for angina leading to coronary revascularization.[57] The LoDoCo2 trial also compared low dose colchicine with placebo: cardiovascular death, MI, and revascularization were significantly reduced in the colchicine arm.[58] However, the effect differed between geographical areas (non-significant in the Netherlands). There was also a non-significant increase in non-cardiovascular death in the colchicine arm. COLCOT and LoDoCo2 both excluded patients with severe HF. Colchicine is not currently incorporated into guideline-recommended therapy but could offer opportunities for future research.

## Conclusion

ACE inhibitors, beta-blockers, and MRAs are the mainstay of treatment in patients with LVSD post MI; there may also be a role for anticoagulation (evidence particularly for rivaroxaban). For patients with chronic HF, there are landmark trials showing the prognostic value of sacubitril-valsartan and SGLT-2 inhibitors (empagliflozin and dapagliflozin). However, sacubitril-valsartan has not yet been shown to be superior to an ACE inhibitor in reducing cardiovascular mortality and HF events in patients with LVSD post MI. Large RCTs evaluating SGLT-2 inhibitors in LVSD post MI are ongoing.

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