

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 $\leq 40\%$) 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 captopril¹³ 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

Lisinopril¹⁵ and captopril¹⁶ 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 trials²² found that ivabradine does reduce heart rate and

Table I 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 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 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 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 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 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 MI⁴⁰ 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 inter-current 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 HFrEF 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 ($\leq 40\%$) 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 (PARADISE-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 SGLT-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 SGLT-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 SGLT-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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References

1. Torabi A, Cleland JG, Khan NK, et al. The timing of development and subsequent clinical course of heart failure after a myocardial infarction. *Eur Heart J*. 2008;29:859–870. doi:10.1093/eurheartj/ehn096
2. Kober L, Torp-Pedersen C, Pedersen OD; on behalf of the TRACE study group. Importance of congestive heart failure and interaction of congestive heart failure and left ventricular systolic function on prognosis in patients with acute myocardial infarction. *Am J Cardiol*. 1996;78:1124–1128. doi:10.1016/S0002-9149(96)00576-0
3. National Institute for Health and Clinical Excellence NG185 – acute Coronary Syndromes. London: NICE; 2020. Available from: [nice.org.uk/guidance/ng185](https://www.nice.org.uk/guidance/ng185). Accessed July 1, 2021.
4. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730–1737. doi:10.1136/bmj.318.7200.1730
5. Houghton T, Freemantle N, Cleland JG. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. *Eur J Heart Fail*. 2000;2:333–340. doi:10.1016/S1388-9842(00)00100-8
6. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction inpatients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390. doi:10.1016/S0140-6736(00)04560-8
7. Flather MD, Yusuf S, Kober L. Long term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355:1575–1581. doi:10.1016/S0140-6736(00)02212-1
8. McDonagh TA, Metra M, Adamo M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:2129–2200. doi:10.1093/eurheartj/ehw128
9. Munkhaugen J, Ruddox V, Halvorsen S, et al. BETA-blocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI): rationale and design of a prospective, randomized, open, blinded end point study. *Am Heart J*. 2019;208:37–46.
10. Kristensen AMD, Bovin A, Zwisler AD, et al. Design and rationale of the Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction: study protocol for a randomized controlled trial. *Trials*. 2020;21:415. doi:10.1186/s13063-020-4214-6
11. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 1995;333:1670–1676. doi:10.1056/NEJM199512213332503
12. Study TA. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet*. 1993;342:821–828.
13. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669–677. doi:10.1056/NEJM199209033271001
14. Wu J, Hall AS; Gale CP on behalf of the AIREX Study Investigators. Long-term survival benefit of ramipril in patients with acute myocardial infarction complicated by heart failure. *Heart*. 2021;107:389–395. doi:10.1136/heartjnl-2020-316823
15. Vecchio C. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet*. 1994;343:1115–1122.
16. Collins R, Peto R, Flather M. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet*. 1995;345:669–685.
17. Dickstein K, Kjekshus J. Effects of losartan captopril on mortality morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. *Lancet*. 2002;360:752–760. doi:10.1016/S0140-6736(02)09895-1

18. Pfeffer MA, McMurray JJ, Velazquez EJ, et al.; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 2003;349:1893–1906. doi:10.1056/NEJMoa032292
19. Pitt B, Remme W, Zannad F, et al.; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348:1309–1321. doi:10.1056/NEJMoa030207
20. Miller RJ, Howlett JG. Retrospective review of in hospital use of mineralocorticoid receptor antagonists for high risk patients following myocardial infarction. *BMC Cardiovasc Disord.* 2015;15:46. doi:10.1186/s12872-015-0033-1
21. Swedberg K, Komajda M, Böhm M, et al.; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–885. doi:10.1016/S0140-6736(10)61198-1
22. Wang B, Zhang X, Chen J, et al. Effectiveness and safety of ivabradine in the treatment of acute myocardial infarction: a systematic review and meta-analysis. *Ann Palliat Med.* 2021;10:4523–4531. doi:10.21037/apm-21-563
23. Taylor AL, Ziesche S, Yancy C, Carson P; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med.* 2004;351:2049–2057. doi:10.1056/NEJMoa042934
24. Farag M, Mabote T, Shoaib A, et al. Hydralazine and nitrates alone or combined for the management of chronic heart failure: a systematic review. *Int J Cardiol.* 2015;196:61–69. doi:10.1016/j.ijcard.2015.05.160
25. Wiggers H, Køber L, Gislason G, et al. The DANish randomized, double-blind, placebo controlled trial in patients with chronic HEART failure (DANHEART): a 2 × 2 factorial trial of hydralazine-isosorbide dinitrate in patients with chronic heart failure (H-HeFT) and metformin in patients with chronic heart failure and diabetes or prediabetes (Met-HeFT). *Am Heart J.* 2021;231:137–146.
26. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057. doi:10.1056/NEJMoa0904327
27. Bulluck H, Chan MHH, Paradies V, et al. Incidence and predictors of left ventricular thrombus by cardiovascular magnetic resonance in acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: a meta-analysis. *J Cardiovasc Magn Reson.* 2018;20:72. doi:10.1186/s12968-018-0494-3
28. Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Report of the Sixty Plus Reinfarction Study Research Group. *Lancet.* 1980;2:989–994.
29. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med.* 1990;323:147–152. doi:10.1056/NEJM199007193230302
30. Jonker JJ, Vanbergen PF. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. *Lancet.* 1994;343:499–503.
31. Moulson N, LaHaye SA, Bertrand OF, MacHaalany J. Prophylactic warfarin post anterior ST-elevation myocardial infarction: a systematic review and meta-analysis. *Cardiovasc Revasc Med.* 2017;18:559–564. doi:10.1016/j.carrev.2017.05.002
32. Mega JL, Braunwald E, Wiviott SD, et al.; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;366:9–19. doi:10.1056/NEJMoa1112277
33. Eikelboom JW, Connolly SJ, Bosch J, et al.; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330. doi:10.1056/NEJMoa1709118
34. Connolly SJ, Eikelboom JW, Bosch J, et al.; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391:205–218.
35. Zannad F, Anker SD, Byra WM, et al.; COMMANDER HF Investigators. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med.* 2018;379:1332–1342. doi:10.1056/NEJMoa1808848
36. Nygaard MH, Hvas AM, Grove EL. Efficacy and safety of oral anticoagulants in patients with systolic heart failure in sinus rhythm: a systematic review and meta-analysis of randomized controlled trials and cohort studies. *TH Open.* 2020;4:e383–e392. doi:10.1055/s-0040-1720961
37. Alexander JH, Becker RC, Bhatt DL, et al.; APPRAISE Steering Committee and Investigators. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. *Circulation.* 2009;119:2877–2885.
38. Alexander JH, Lopes RD, James S, et al.; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011;365:699–708. doi:10.1056/NEJMoa1105819
39. National Institute for Health and Care Excellence. *Rivaroxaban for Preventing Adverse Outcomes After Acute Management of Acute Coronary Syndrome.* Technology appraisal guidance [TA335]; 2015.
40. Hayiroğlu Mİ, Keskin M, Uzun AO, et al. Predictors of in-hospital mortality in patients with ST-segment elevation myocardial infarction complicated with cardiogenic shock. *Heart Lung Circ.* 2019;28:237–244. doi:10.1016/j.hlc.2017.10.023
41. de Silva R, Nikitin NP, Witte KK, et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. *Eur Heart J.* 2006;27:569–581. doi:10.1093/eurheartj/ehi696
42. Zachariah D, Brown R, Kanagala P, et al. The impact of age and chronic kidney disease on secondary prevention post-primary percutaneous coronary intervention. *QJM.* 2014;107:185–192. doi:10.1093/qjmed/hct222
43. Clark AL, Kalra PR, Petrie MC, Mark PB, Tomlinson LA, Tomson CR. Change in renal function associated with drug treatment in heart failure: national guidance. *Heart.* 2019;105:904–910.
44. McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371:993–1004. doi:10.1056/NEJMoa1409077
45. Pellicori P, Urbinati A, Shah P, et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? *Eur J Heart Fail.* 2017;19:768–778. doi:10.1002/ehf.788
46. Solomon SD, McMurray JJV, Anand IS, et al.; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2019;381:1609–1620. doi:10.1056/NEJMoa1908655
47. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117–2128. doi:10.1056/NEJMoa1504720
48. McMurray JJV, Solomon SD, Inzucchi SE, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381:1995–2008. doi:10.1056/NEJMoa1911303
49. Packer M, Anker SD, Butler J, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383:1413–1424. doi:10.1056/NEJMoa2022190

50. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121–128. doi:10.1016/S0140-6736(20)30748-0
51. Teerlink JR, Diaz R, Felker GM, et al.; GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384:105–116. doi:10.1056/NEJMoa2025797
52. Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. *Eur J Heart Fail*. 2021;23:1040–1048. doi:10.1002/ejhf.2191
53. Presented by Dr. Marc Pfeffer at the American College of Cardiology Virtual Annual Scientific Session (ACC 2021), May 15, 2021.
54. National Institute for Health and Clinical Excellence QS103. Chronic heart failure in adults. London: NICE; 2018. Available from: [nice.org.uk/guidance/qs9/chapter/List-of-quality-statements](https://www.nice.org.uk/guidance/qs9/chapter/List-of-quality-statements). Accessed October 26, 2021.
55. Clinicaltrials.gov. EMPACT-MI: a Streamlined, Multicentre, Randomised, Parallel Group, Double-blind Placebo-controlled Superiority Trial to Evaluate the Effect of EMPagliflozin on Hospitalisation for Heart Failure and Mortality in Patients With aCuTe Myocardial Infarction. Available from: <https://clinicaltrials.gov/ct2/show/NCT04509674>. Accessed July 1, 2021.
56. Clinicaltrials.gov. Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack (DAPA-MI). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT04564742>. Accessed July 1, 2021.
57. Tardif J-C, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497–2505. doi:10.1056/NEJMoa1912388
58. Nidorf SM, Fiolet ATL, Mosterd A, et al.; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383:1838–1847. doi:10.1056/NEJMoa2021372

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