Medicines Management Programme:

Preferred Drugs

Angiotensin-Converting Enzyme (ACE) inhibitors

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Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACE 2	Angiotensin-converting enzyme 2
ADR	Adverse drug reaction
AHA	American Heart Association
ARNI	Angiotensin receptor-neprilysin inhibitors
ARB	Angiotensin-II receptor blocker
BIHS	British and Irish Hypertension Society
BP	Blood pressure
CCB	Calcium channel blocker
CDS	Community drug scheme
CKS	Clinical knowledge summaries
CV	Cardiovascular
DBP	Diastolic blood pressure
DDD	Defined daily dose
DPS	Drugs Payment Scheme
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GMS	General Medical Services
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
LTI	Long Term Illness
MAP	Mean arterial pressure
MMP	Medicines Management Programme
mTOR	Mammalian target of rapamycin
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
PCRS	Primary Care Reimbursement Services
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
SBP	Systolic blood pressure
SGLT2	Sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

Acknowledgements

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1. Purpose

Ramipril has been the Health Service Executive's Medicines Management Programme (HSE-MMP) preferred Angiotensin-Converting Enzyme (ACE) inhibitor since September 2013.[1] The purpose of this report is to review the choice of preferred ACE inhibitor in light of the current available evidence.

The MMP aims to promote safe, effective and cost-effective prescribing. The Preferred Drugs Initiative identifies a single "preferred drug" within a therapeutic drug class, and offers prescribers useful guidance on selecting, prescribing and monitoring these drugs for a particular condition. In this case, the use of ACE inhibitors in the management of patients with cardiovascular conditions, in particular hypertension and heart failure in adults is reviewed.

Prescribers are encouraged to choose the preferred drug, when initiating an ACE inhibitor and when there is a need to change from one ACE inhibitor to another, in the treatment of hypertension or heart failure.

This report should be used in conjunction with clinical judgement and decision making appropriate to the individual patient. Prescribers should refer to sources such as the Summary of medicinal Product Characteristics (SmPC) to inform decision-making concerning individual patients.

2. Definitions

For the purpose of this report, the associated ingredient cost refers to the reimbursed cost of the named ACE inhibitor as listed on the HSE-Primary Care Reimbursement Service's (PCRS) website (www.pcrs.ie). ACE inhibitors reimbursed for the treatment of hypertension or heart failure are included in this review.

The Community Drug Schemes (CDS) referred to throughout this document include the Drugs Payment Scheme (DPS), Long Term Illness (LTI) scheme and the General Medical Services (GMS) scheme. Data in relation to the CDS is limited by its inability to capture prescriptions

that are solely funded by the patient, and therefore not reimbursed under any of the state funded CDS e.g. prescriptions that fall below the co-payment threshold on the DPS.

When two or more preparations of the same drug are listed (e.g. where there are different manufacturers/suppliers), the least expensive preparation licensed for the relevant indications has been selected for the evaluation. Costs are correct as of 11/02/2022.

3. Angiotensin-Converting Enzyme Inhibitors

In plasma and tissue, ACE catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin.[2] Angiotensin II is involved in the renin-angiotensin-aldosterone system, which regulates blood pressure (BP), sodium and water homeostasis by the kidneys, and cardiovascular (CV) function. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a direct vasoconstrictor effect.[3] Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation. [2]

There are seven licensed and reimbursed ACE inhibitors available in Ireland under the CDS; enalapril, lisinopril, perindopril, quinapril, ramipril, trandolapril and zofenopril.

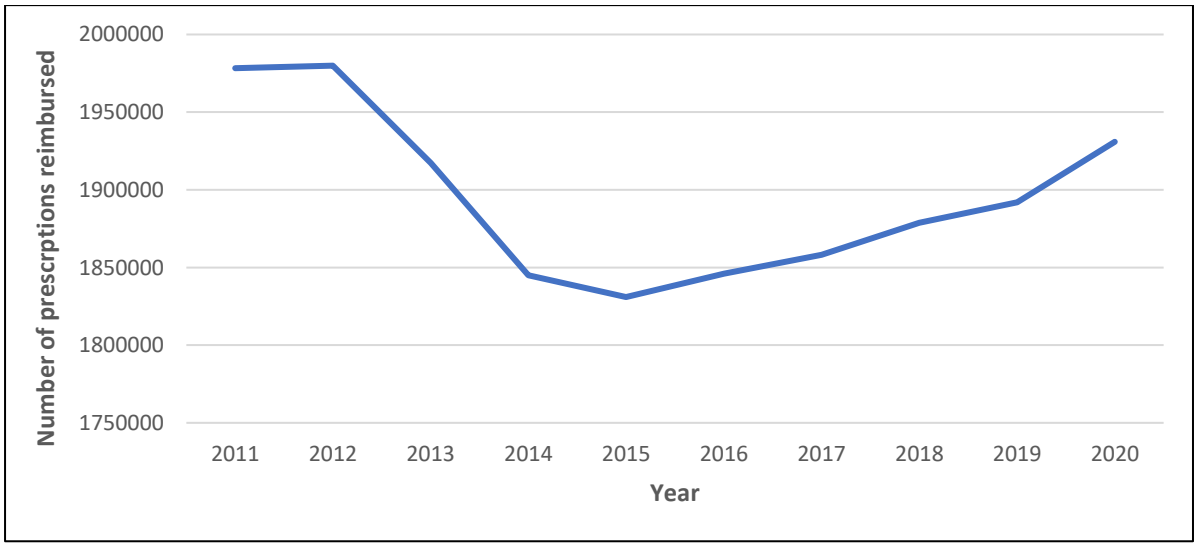

Figure 1: Combined total number of prescriptions per annum for ACE inhibitors reimbursed under community drug schemes 2011-2020

Figure 1 illustrates that the number of prescriptions for ACE inhibitors reimbursed per annum under the CDS was stable in 2011 and 2012. The number decreased from 2013 to 2015. There has been steady growth in the number of prescriptions from 2015 until 2020.[4]

Total expenditure (inclusive of ingredient cost and pharmacy dispensing fees) in 2020 on ACE inhibitors under the CDS was €16.3 million.[4]

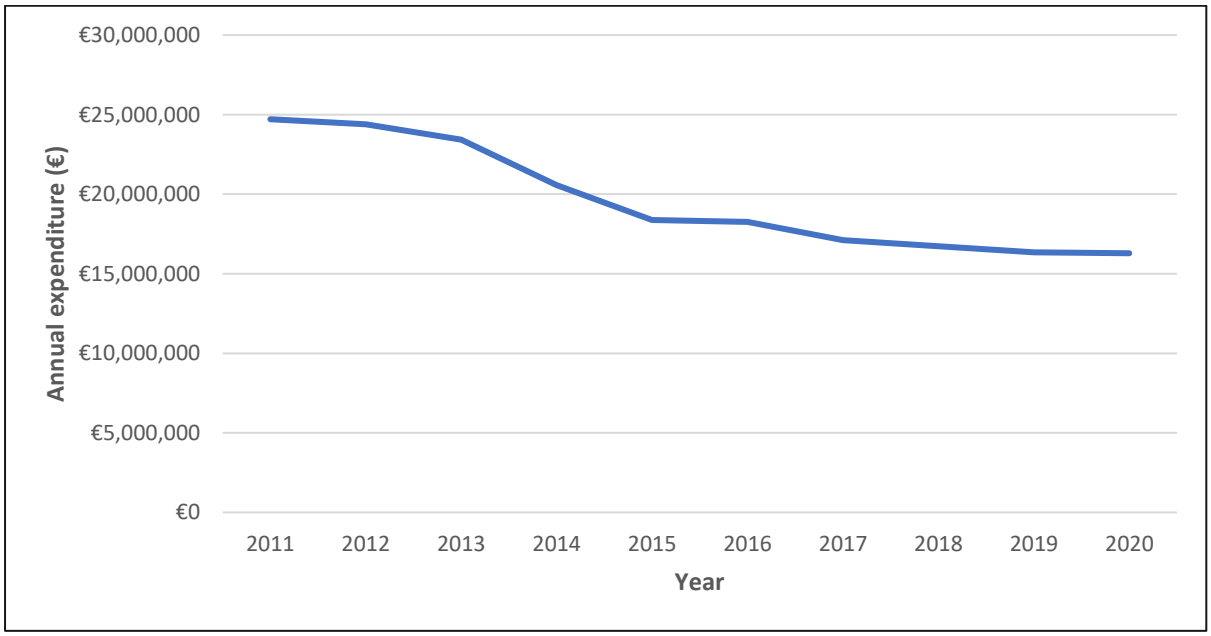

Figure 2: Annual Expenditure on ACE inhibitors reimbursed under community drug schemes 2011-2020

Figure 2 illustrates that there has been a decline in expenditure on ACE inhibitors from 2011 (€24.7 million) to 2020 (€16.3 million) under the CDS. Expenditure on ACE inhibitors has decreased following the introduction of generic substitution and reference pricing from 2014 onwards.[4]

4. Preferred Angiotensin-Converting Enzyme inhibitor

Based on the current evidence, ramipril is the MMP's preferred ACE inhibitor for the treatment of hypertension and heart failure.

5. Selection criteria

A number of key criteria were considered in the MMP preferred ACE inhibitor selection process:

- **Licensed therapeutic indications**
- **Clinical outcome data**
- **Clinical guidelines**
- **Adverse drug reactions**
- **Contraindications and cautions**
- **Drug interactions**
- **Patient factors**
- **Cost**
- **National prescribing trends**

5.1 Licensed therapeutic indications

A broad license in terms of therapeutic indication(s) relative to other drugs in this class is considered advantageous. As the focus of this guidance is the use of ACE inhibitors in hypertension and heart failure, the preferred ACE inhibitor should be licensed, at a minimum, for these two indications. Additional licensed therapeutic indications incorporating other patient groups (e.g. renal disease) are welcome.

All seven ACE inhibitors are licensed for the treatment of hypertension.[2, 5-26] Enalapril, lisinopril, perindopril, quinapril, ramipril and trandolapril, are also licensed in heart failure.[2, 5-8, 11-26] Lisinopril and ramipril are licensed in renal disease.[5-8, 23-26] Lisinopril, ramipril and zofenopril are licensed in acute myocardial infarction.[5-10, 23-26] Perindopril and ramipril are licensed for coronary artery disease.[20-26]

Ramipril has the broadest range of licensed indications of all the ACE inhibitors included in this review.[23-26] These differences in the licensing particulars were considered significant in enabling our recommendation for a single preferred drug for ACE inhibitors. The licensed indications for reimbursed ACE inhibitors are summarised in Table 1.

Table 1: Licensed therapeutic indications* of ACE inhibitors

Drug	Hypertension	Heart failure	Renal disease/ nephropathy	Acute myocardial infarction	Coronary artery disease
Enalapril [11-14]	✓	✓			
Lisinopril [5-8]	✓	✓	✓	✓	
Perindopril [20-22]	✓	✓			✓
Quinapril [2, 17-19]	✓	✓			
Ramipril [23-26]	✓	✓	✓	✓	✓
Trandolapril [15, 16]	✓	✓			
Zofenopril [9, 10]	✓			✓	

*Please refer to individual SmPC for full prescribing information

All licensed ACE inhibitors are indicated for the treatment of hypertension. All, with the exception of zofenopril, are also licensed in heart failure. Ramipril has the broadest license in terms of therapeutic indications relative to other drugs within the ACE inhibitor class.

5.1.1 Hypertension

Hypertension is defined as persistently raised arterial BP and is one of the most important treatable causes of premature morbidity and mortality. It is a major risk factor for stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Hypertension is more common in advancing age, in women aged between 65–74 years and in people of black African or African-Caribbean origin. Other risk factors include social deprivation, lifestyle factors, anxiety, and emotional stress. [27]

The global prevalence of hypertension was estimated to be 1.13 billion in 2015 and the overall prevalence of hypertension in adults is around 30–45%. It is estimated that the number of people with hypertension will increase by 15–20% by 2025, reaching close to 1.5 billion. [28]

5.1.2 Heart Failure

Heart failure is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. It is characterised by symptoms such as shortness of breath, persistent coughing or wheezing, ankle swelling, reduced exercise tolerance, and fatigue. These symptoms may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles, and pulmonary oedema. [27, 29]

The risk of heart failure is greater in men, smokers and people with diabetes, and increases with age. [27]

The most common cause of heart failure is coronary heart disease; however, patients of African or Afro-Caribbean origin are more likely to develop heart failure secondary to hypertension. In addition to coronary heart disease, heart failure often co-exists with other co-morbidities such as chronic kidney disease, atrial fibrillation, hypertension, dyslipidaemia, obesity, diabetes mellitus, and chronic obstructive pulmonary disease. Patients with co-morbidities have a worse prognosis, and the presence of atrial fibrillation or chronic kidney disease affects the management of heart failure in these patients. Complications of heart failure include chronic kidney disease, atrial fibrillation, depression, cachexia, sexual dysfunction, and sudden cardiac death. [27]

Patients with heart failure can be classified as either having a reduced, mildly reduced or preserved ejection fraction; all three types present with signs and symptoms of heart failure. In heart failure with reduced ejection fraction, the left ventricle loses its ability to contract normally and therefore patients present with an ejection fraction of less than or equal to 40%. It is only in heart failure patients with reduced ejection fraction that therapies have been shown to reduce both morbidity and mortality.[29]

In heart failure with preserved ejection fraction, patients generally do not have a dilated left ventricle, but instead often have an increase in left ventricular wall thickness and/or increased left atrial size as a sign of increased filling pressures. Most have additional evidence of impaired left ventricular filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of heart failure in these patients. Patients present with an ejection fraction greater than or equal to 50%.[29]

Patients with a left ventricular ejection fraction in the range of 41-49% are now defined as having mildly reduced ejection fraction. These patients most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction. [29]

The New York Heart Association (NYHA) functional classification tool is used to define the progression of chronic heart failure according to severity of symptoms and limitation to physical activity. Heart failure is considered to be stable or chronic when symptoms remain unchanged for at least one month despite optimal management. [29]

5.2 Clinical Outcome Data

When the HSE-MMP initial review of ACE inhibitors was undertaken in 2013, consideration was given to pivotal clinical trials and evidence available at that time.[1] This review evaluates updated evidence since the publication of the 2013 version of the preferred drug document for ACE inhibitors. There have been no new clinical trials identified since 2013 which compare ACE inhibitors in the treatment of hypertension and heart failure.

5.2.1 Meta-analyses and systematic reviews in the treatment of hypertension

Systematic reviews and meta-analyses which utilise pooled data from clinical trials, provide a means of assessing the general and comparative efficacy of ACE inhibitors, and were considered as part of the review process.

No new systematic reviews or meta-analyses comparing efficacy of ACE inhibitors in the treatment of hypertension were identified.

5.2.2 Meta-analyses and systematic reviews in the treatment of heart failure

5.2.2.1 Sun et al. (2016)

A network meta-analysis by Sun et al. (2016) was conducted to determine the comparative efficacy of ACE inhibitors in patients with heart failure with respect to the primary outcomes of all-cause mortality, stroke volume and ejection fraction. The secondary outcomes measured were blood pressure, cough, deterioration of renal function and gastrointestinal discomfort. Twenty-nine studies were included in the meta-analysis. Pairwise comparisons and network comparisons were utilised as part of the analysis. [30]

In this analysis, all-cause mortality included pulmonary oedema, ventricular fibrillation, acute myocardial infarction, complications after surgical intervention for colon cancer during the study, sudden death (reason unknown), stroke, progressive renal insufficiency, and severe heart failure. Based on thirteen studies (n=1022) analysing four drugs (captopril, enalapril, lisinopril, and ramipril) and placebo, lisinopril was associated with higher all-cause mortality compared with placebo or ramipril. No significant differences were found in the other possible comparisons. [30]

In six studies (n=423) which analysed the effect of three drugs (captopril, enalapril, and lisinopril) and placebo on stroke volume, all network comparisons were possible and some pairwise comparisons were possible. Pairwise meta-analyses indicated that captopril groups significantly improved stroke volume compared with placebo groups. [30]

In five studies (n=453) which analysed the effect of three drugs (captopril, enalapril, and lisinopril) and placebo on ejection fraction, all network comparisons were possible and some pairwise comparisons were possible. No significant differences were found among the possible interventions with regard to ejection fraction. [30]

BP outcomes were reported as systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). In these analyses, all network comparisons were possible and some pairwise comparisons were possible. Based on nine studies (n=606) with four drugs (captopril, enalapril, lisinopril, and trandolapril) and placebo, enalapril significantly reduced SBP compared to placebo. Based on seven studies (n=563) with four drugs (captopril, enalapril, lisinopril, and trandolapril) and placebo, no significant differences in DBP were found among the possible interventions. Based on nine studies (n=427) with two drugs (enalapril and captopril) and placebo, no significant differences in MAP were found among the possible interventions. [30]

Based on four studies (n=341) with two drugs (captopril and enalapril) and placebo, both captopril and enalapril were associated with a higher incidence of cough compared to placebo. There was no significant difference in cough between captopril and enalapril. [30]

Based on four studies (n=713) with three drugs (captopril, enalapril, and lisinopril) and placebo, captopril was associated with a lower incidence of renal function deterioration compared with enalapril. No significant differences were found in the other possible comparisons. [30]

Based on six studies (n=777) with three drugs (captopril, enalapril, and lisinopril) and placebo, no significant differences were found among the possible interventions regarding gastrointestinal discomfort. [30]

The study concluded that when considering factors such as increased ejection fraction, stroke volume, and decreasing MAP, the results suggest that enalapril was the most effective ACE inhibitor. However, enalapril was also associated with the highest incidence of cough, as well as renal function deterioration and gastrointestinal discomfort. An increase in all-cause mortality combined with a limited effect on reducing systolic and diastolic blood pressure made lisinopril the least favourable among the ACE inhibitors evaluated. Ramipril was associated with the lowest incidence of all-cause mortality. Trandolapril ranked first in reducing systolic and DBP. The author's concluded that further studies should be performed to confirm the results. [30]

Limitations include that some important outcomes such as re-hospitalization and cardiac death were not included in this analysis, most studies were single-centre studies with few performed in Asia and none in Africa, the sample size was small (ramipril was only included in one study) and all outcomes did not include all ACE inhibitors. [30]

5.2.2.2 Chatterjee et al. (2013)

A network meta-analysis by Chatterjee et al. (2013), available in abstract form, analysed ten randomised controlled trials. [31]

No credible differences were found between the different ACE inhibitors for the risk of death, sudden cardiac death, death due to pump failure, rehospitalisation or drug discontinuation.[31]

Due to the fact that this study was only available in abstract form, information is limited as to which ACE inhibitors were included, how the network meta-analysis was undertaken and how results were analysed.

Overall, limited additional evidence was identified in relation to clinical outcome data for the use of ACE inhibitors in the treatment of hypertension and heart failure since the previous review of ACE inhibitors was undertaken in 2014.

There were no significant differences in clinical efficacy noted among various ACE inhibitors when compared for the treatment of hypertension and heart failure.

5.3 Clinical guidelines for the treatment of hypertension and heart failure

5.3.1 Hypertension

International clinical guidelines for the management of hypertension along with available Irish guidance (Irish College of General Practitioners [ICGP]) were considered in the evaluation process, as shown in table 2. Table 3 contains practical clinical guidance in the management of hypertension.

Table 2: Clinical guidelines for the treatment of hypertension

Review body	Guideline	Year	Initial drug treatment options	Preferred ACE inhibitor
Irish College of General Practitioners[32]	Cardiovascular disease: prevention in general practice	2021	• ACE inhibitor or an ARB for patients with type 2 diabetes and of any age or family origin, or aged < 55 years but not of black African/African-Caribbean family origin. • CCB for patients aged > 55 years and do not have type 2 diabetes, or are of black African/African-Caribbean family origin (any age).	None
National Institute for Health and Care Excellence[33]	Hypertension in adults	2019	• ACE inhibitor or an ARB for patients with type 2 diabetes and of any age or family origin, or aged < 55 years but not of black African/African-Caribbean family origin. • CCB for patients aged > 55 years and do not have type 2 diabetes, or are of black African/African-Caribbean family origin (any age).	None
European Society of Hypertension and European Society of Cardiology[28]	Arterial hypertension	2018	• Dual combination to include an ACE inhibitor or an ARB and CCB or a diuretic. • Consider monotherapy in low grade 1 hypertension (systolic BP < 150 mmHg), or in very old (≥ 80 years) or frailer patients.	None
International Society of Hypertension[34]	Global hypertension	2020	• Dual low-dose combination of an ACE inhibitor or an ARB and a CCB. • Ideally single-pill combination therapy.	None
American College of Cardiology and American Heart Association[35]	High blood pressure in adults	2017	• First-line agents include ACE inhibitor/ARB, CCBs or thiazide diuretics. • Initiation with a single antihypertensive drug is reasonable in adults with stage 1 hypertension. • Initiation with two first-line agents or a fixed-dose combination is recommended in adults with stage 2 hypertension (≥ 140/90 mmHg).	None

ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-II receptor blocker; CCB: Calcium channel blocker.

Table 3: Clinical practice guidelines for the treatment of hypertension

Review body	Year	Initial drug treatment option	Preferred ACE inhibitor
Clarity's Diagnosis and Treatment Guidance[36]	2020	• For people aged under 55 years who are not of black African/Caribbean family origin, offer an ACE inhibitor or an ARB. • For people aged 55 years or over and people of black African/Caribbean family origin (any age), offer a CCB.	• Hypertension and heart failure: enalapril, lisinopril, ramipril, and trandolapril • Diabetes and hypertension: enalapril, lisinopril, perindopril, ramipril, or trandolapril

ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-II receptor blocker; CCB: Calcium channel blocker

Irish College of General Practitioners

ICGP guidelines *Cardiovascular disease: prevention in general practice* (2021), states that the key messages on the management of high BP are based on National Institute for Health and Care Excellence (NICE) guideline (NG136) on clinical management of primary hypertension in adults (2019). ICGP recommends for step one treatment offering an ACE inhibitor or an ARB to adults who:

- have type 2 diabetes and are of any age or family origin, or
- are aged under 55 years but not of black African or African-Caribbean family origin.

A calcium-channel blocker (CCB) should be offered to adults starting step one antihypertensive treatment who are:

- aged 55 years or over and do not have type 2 diabetes or,
- of black African or African-Caribbean family origin and do not have type 2 diabetes (of any age).

If hypertension is not controlled in adults taking step one treatment of an ACE inhibitor or ARB, offer the choice of a CCB or a thiazide-like diuretic. If hypertension is not controlled in adults taking step one treatment of a CCB, offer an ACE inhibitor, an ARB or a thiazide-like diuretic.

The ICGP guideline states that emphasis should be given to avoidance of co-prescription of ACE inhibitors and ARBs and the importance of checking potassium and creatinine levels within two weeks of initiating or increasing the dose of ACE/ARB treatment. The guideline

also acknowledges SARS-CoV-2 virus in relation to the use of ACE inhibitors and ARBs in the treatment of hypertension. Angiotensin-converting enzyme 2 (ACE2) is a protein that sits on the surface of many types of cells in the human body, including in the heart, gut, lungs and inside the nose. Studies in animals have suggested that ACE inhibitors and ARBs may up-regulate ACE2 expression, thus increasing the availability of target molecules for SARS-CoV-2. These considerations have led to speculation that ACE inhibitors and ARBs might be harmful in such patients should they contract COVID-19. Three observational studies which provided data about whether ACE inhibitors and ARBs are indeed harmful in the context of the COVID-19 pandemic studies were reviewed. Their message was consistent – there was no evidence of harm with continued use of ACE inhibitors and ARBs in this setting. In the BRACE CORONA study, the first randomised controlled trial assessing the role of continuing versus stopping ACE inhibitors and ARBs in patients with COVID-19, the safety of ACE inhibitors and ARBs in COVID-19 patients was further confirmed. [32]

This guideline does not recommend a particular ACE inhibitor to use in the treatment of hypertension.

National Institute for Health and Care Excellence

NICE guidance (NG136) *Hypertension in adults: diagnosis and management* (2019), recommends offering an ACE inhibitor or an ARB to adults on step 1 treatment where clinic BP is ranging from 140/90 mmHg to 159/99 mmHg and subsequent ambulatory BP monitoring daytime average BP or home BP monitoring average BP is ranging from 135/85 mmHg to 149/94 mmHg who:

- have type 2 diabetes and are of any age or family origin, or
- are aged under 55 years but not of black African or African-Caribbean family origin.

A CCB should be offered to adults starting step 1 antihypertensive treatment who are:

- aged 55 years or over and do not have type 2 diabetes or,
- of black African or African-Caribbean family origin and do not have type 2 diabetes (of any age).

If hypertension is not controlled in adults taking step 1 treatment of an ACE inhibitor or ARB, offer the choice of a CCB or a thiazide-like diuretic. If hypertension is not controlled in adults taking step 1 treatment of a CCB, offer an ACE inhibitor, an ARB or a thiazide-like diuretic.
If hypertension is not controlled in adults of black African or African–Caribbean family origin who do not have type 2 diabetes taking step 1 treatment, consider an ARB, in preference to an ACE inhibitor, in addition to step 1 treatment. [33]

The guidance does not recommend a particular ACE inhibitor to use in the treatment of hypertension.

European Society of Cardiology and the European Society of Hypertension

The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) *Guidelines for the management of arterial hypertension* (2018) recommend the initiation of treatment in most patients with a single-pill combination comprising two drugs, to improve the speed, efficiency, and predictability of BP control. Preferred two-drug combinations are a renin-angiotensin system (RAS) blocker with a CCB or a diuretic. The guidelines recommend using monotherapy only for low-risk patients with stage 1 hypertension whose systolic blood pressure is < 150 mmHg, very high-risk patients with high-normal BP, or frail older patients. If BP is not controlled by a two-drug single-pill combination, the use of a three-drug single-pill combination comprising a RAS blocker, a CCB and a diuretic is recommended. [28]

The guideline states that blockers of the RAS, which include both ACE inhibitors and ARBs, have similar effectiveness as each other and other major drug classes such as CCB, diuretics and beta-blockers on major cardiovascular events and mortality outcomes. [28]

The guideline does not state a preferred ACE inhibitor for the treatment of hypertension.

International Society of Hypertension

The International Society of Hypertension *Global Hypertension Practice Guidelines* (2020), recommends for the initial treatment of hypertension (i.e. Step 1), a dual low-dose combination of an ACE inhibitor or an ARB and a CCB for optimal therapy. This escalates to full-dose combination and then the addition of a thiazide-like diuretic.

This guideline does not recommend a particular ACE inhibitor to use in the treatment of hypertension. The guideline states that choice between the two classes of RAS blockers will depend on patient characteristics, availability, costs and tolerability. [34]

American College of Cardiology and American Heart Association

The American College of Cardiology (ACC) and American Heart Association (AHA) task force on clinical practice guidelines for the *Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults* (2017), recommends that for initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs and ACE inhibitors or ARBs.[35]

The guideline does not recommend a preferred ACE inhibitor for the treatment of hypertension.

British and Irish Hypertension Society

The British and Irish Hypertension Society (BIHS) guidelines for hypertension management refer to the NICE guideline (NG136): *Hypertension in Adults: Diagnosis and Management*. BIHS have not endorsed the ESC/ESH guideline or the NICE guideline but recognises that colleagues in the Society and beyond are likely to follow NICE guidelines in clinical practice.[37]

Clarity's Diagnosis and Treatment Guidance

Clarity's Diagnosis and Treatment Guidance state the treatment options for patients with hypertension. They recommend offering an ACE inhibitor or an ARB to adults who:

- have type 2 diabetes and are of any age or family origin, or
- are aged under 55 years but not of black African or African-Caribbean family origin.

A calcium-channel blocker (CCB) should be offered to adults starting step 1 antihypertensive treatment who are:

- aged 55 years or over and do not have type 2 diabetes or,
- of black African or African-Caribbean family origin and do not have type 2 diabetes (of any age).

The guidance states that the choice of ACE inhibitor usually depends on the person's co-morbidities, local recommendations, and cost. Where possible, prescribe a drug that is taken only once a day and prescribe non-proprietary drugs where these are appropriate and minimise cost.

The guidance recommends enalapril, lisinopril, ramipril, and trandolapril as preferred ACE inhibitors in patients with hypertension and heart failure. In patients with diabetes and hypertension, enalapril, lisinopril, perindopril, ramipril, or trandolapril may be preferred ACE inhibitors. [36]

Many of the clinical guidelines outlined above recommend first line treatment options based on a range of clinical features including; presence of type 2 diabetes mellitus, ethnic origin and age. The MMP does not support the use of patient age as a suitable criterion for selection of first-line antihypertensive agents, as the data is not conclusive.

Clinical guidelines do not identify a preferred ACE inhibitor for the treatment of hypertension.

5.3.2. Heart Failure

International clinical guidelines for the management of heart failure along with available Irish guidance (ICGP) were considered in the evaluation process, as shown in table 4. Table 5 contains practical clinical guidance in the management of heart failure.

Table 4: Clinical guidelines for the treatment of heart failure

Review body	Guideline	Year	Initial drug treatment options	Preferred ACE inhibitor
Irish College of General Practitioners (ICGP)[32]	Heart failure in general practice	2019	• ACE inhibitor + beta-blocker.	None
National Institute for Health and Care Excellence [38]	Chronic heart failure in adults	2018	• ACE inhibitor + beta-blocker.	None
American College of Cardiology, American Heart Association and the Heart Failure Society of America [39]	Management of Heart Failure	2017	• ACE inhibitor/ARB/ARNI + beta blocker. • Diuretics as needed.	Enalapril, lisinopril, perindopril, quinapril, ramipril, trandolapril
European Society of Cardiology [29]	Acute and Chronic Heart Failure	2021	• ACE inhibitor/ARNI* + beta-blocker + MRA + dapagliflozin/empagliflozin	None

*Use ARNI instead of ACE inhibitor only in suitable patients who remain symptomatic on ACE inhibitor, beta-blocker, and MRA therapies

ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-II receptor blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; CCB: Calcium channel blocker; MRA: Mineralcorticoid receptor antagonist

Table 5: Clinical practice for the treatment of heart failure:

Review body	Year	Initial drug treatment option	Preferred ACE inhibitor
Clarity's Diagnosis and Treatment Guidance [40]	2022	**Confirmed heart failure with reduced ejection fraction:** • If there are symptoms of fluid overload, a diuretic should be prescribed. • An ACE inhibitor + beta-blocker + aldosterone antagonist should be prescribed to reduce morbidity and mortality, one drug at a time to ensure patient is stable. Dapagliflozin should also be prescribed on the advice of a heart failure specialist. For people with **confirmed heart failure with preserved ejection fraction**, a low to medium dose diuretic should be prescribed if necessary and a specialist referral should be arranged.	Captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril or ramipril

ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-II receptor blocker; CCB: Calcium channel blocker.

Irish College of General Practitioners

ICGP guidelines *Heart Failure in General Practice* (2019), recommend an ACE inhibitor, or an ARB if an ACE inhibitor is not tolerated, as part of the initial treatment alongside a beta-blocker for patients diagnosed with heart failure with reduced ejection fraction. The treatments must be titrated to optimal dose before considering other treatments.

This guideline does not recommend a particular ACE inhibitor to use in the treatment of heart failure.[32]

National Institute for Health and Care Excellence

NICE guidance *Chronic heart failure in adults: diagnosis and management* (2018), recommends that an ACE inhibitor and a beta-blocker licensed for heart failure should be offered as first-line treatment to people who have heart failure with reduced ejection fraction.

The guidance recommends starting ACE inhibitor therapy at a low dose and to titrate upwards at short intervals (for example, every two weeks) until the target or maximum tolerated dose is reached. It recommends to measure serum sodium and potassium, and to assess renal function, before and one to two weeks after starting an ACE inhibitor, and after each dose increment. BP should be measured before and after each dose increment. Once the target or maximum tolerated dose of an ACE inhibitor is reached, monitor treatment monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.[38]

This guidance does not recommend a particular ACE inhibitor to use in the treatment of heart failure.

American College of Cardiology, American Heart Association and the Heart Failure Society of America

The ACC/AHA Task Force on Clinical Practice Guidelines and the Heart Failure Society of America focused update of the *Guideline for the Management of Heart Failure* (2017), recommends the clinical strategy of inhibition of the RAS with ACE inhibitors or ARBs

or angiotensin receptor-neprilysin inhibitor (ARNI) in conjunction with evidence-based beta-blocker and aldosterone antagonists in selected patients with chronic heart failure with reduced ejection fraction to reduce morbidity and mortality.

This guideline mentions six licensed ACE inhibitors for the treatment of heart failure; enalapril, lisinopril, perindopril, quinapril, ramipril and trandolapril. However, it does not recommend a particular ACE inhibitor from these options to use in the treatment of heart failure.[39]

European Society of Cardiology

The ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (2021), recommends initial therapy with an ACE inhibitor, a beta-blocker and a mineralocorticoid receptor antagonist (MRA) for patients with symptomatic heart failure with reduced ejection fraction. This has been shown to improve survival, reduce the risk of heart failure hospitalisations and reduce symptoms in patients with heart failure with reduced ejection fraction. An ARNI[i] is suggested as a replacement for ACE inhibitor in suitable patients who remain symptomatic on ACE inhibitor, beta-blocker and MRA therapies. The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to therapy with ACE inhibitor/ARNI with beta-blocker and MRA reduces the risk of cardiovascular death and worsening heart failure in patients with reduced ejection fraction.[29]

This guideline states that ACE inhibitors are recommended in all patients unless contraindicated or not tolerated. They should be uptitrated to the maximum tolerated recommended doses. [29]

This guideline mentions captopril, enalapril, lisinopril, ramipril and trandolapril as ACE inhibitors which have been used in randomised trials in patients with heart failure with reduced ejection fraction. The guideline does not recommend a particular preferred ACE inhibitor to use in the treatment of heart failure.[29]

[i]The treatment of heart failure with an ARNI is outside the scope of this review. Refer to www.hse.ie/yourmedicines for clinical and reimbursement information for sacubitril and valsartan[42].

Clarity's Diagnosis and Treatment Guidance

Clarity's Diagnosis and Treatment Guidance recommends that those with confirmed heart failure with reduced ejection fraction should be prescribed a diuretic if there are symptoms of fluid overload. To reduce morbidity and mortality, an ACE inhibitor, a beta-blocker, and an aldosterone antagonist should be prescribed. One drug should be introduced at a time, adding the second drug once the person is stable on the first drug. Dapagliflozin should also be prescribed on the advice of a heart failure specialist. If the person is still symptomatic despite optimal treatment, a referral for specialist management should be arranged.[40]

For those with confirmed heart failure with preserved ejection fraction, a low to medium dose diuretic should be prescribed if necessary and a specialist referral should be arranged. [40]

This guidance highlights that the ACE inhibitors licensed in the United Kingdom for the treatment of heart failure are captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, and ramipril. [40]

There was no clear preferred ACE inhibitor identified in published clinical guidelines for the treatment of hypertension and heart failure.

5.4 Adverse drug reactions

Adverse effects of ACE inhibitors include:

- **Renal impairment:** Renal function should be monitored 1–2 weeks after starting an ACE inhibitor, after each increase in dose, and regularly throughout treatment. [41, 42]
- **Hyperkalaemia:** Serum electrolytes should be monitored 1–2 weeks after starting an ACE inhibitor, after each increase in dose, and regularly throughout treatment.[41, 42]
- **Cough**: Cough occurs in about 15% of people taking an ACE inhibitor and may occur at any time after starting treatment.[41, 42]
- **Angioedema**: ACE inhibitors can cause a non-allergic drug reaction which can precipitate angioedema.[41, 42]
- **Dizziness and headaches** [41, 42]
- **Hepato-biliary disorders**: This is a very rare adverse effect.[41, 42]
- Other common adverse effects include abdominal discomfort, dyspepsia, diarrhoea, nausea and vomiting, rash (in particular maculo-papular rash), myalgia, muscle spasms, dyspnoea, chest pain, and fatigue.[41, 42]

The common adverse drug reactions (ADRs) [incidence of ≥ 1 in 100 to < 1 in 10] for individual ACE inhibitors are listed in Table 6. A full list of ADRs for each drug can be found in the individual SmPC available at www.hpra.ie.

Table 6: Common adverse drug reactions of individual ACE inhibitors (as per SmPC)

Adverse drug reaction	Enalapril [11-14]	Lisinopril [5-8]	Perindopril [20-22]	Quinapril [2, 17-19]	Ramipril [23-26]	Trandolapril [15, 16]	Zofenopril [9, 10]
Abdominal pain	✓		✓	✓	✓		
Angina pectoris	✓						
Asthenia	✓			✓		✓	
Back pain				✓			
Blood urea increase				✓			
Blurred vision/Visual disturbances	✓		✓				
Bronchitis					✓		
Chest pain	✓			✓	✓		
Constipation			✓				
Cough	✓	✓	✓	✓	✓	✓	✓
Depression	✓						
Diarrhoea	✓	✓	✓	✓	✓		
Digestive disturbances					✓		
Dizziness	✓	✓	✓	✓	✓	✓	✓
Dysgeusia			✓				
Dyspepsia			✓	✓	✓		
Dyspnoea	✓		✓	✓	✓		
Fatigue	✓			✓	✓		✓
Flushing							
Gastrointestinal disorder							

Adverse drug reaction	Enalapril [11-14]	Lisinopril [5-8]	Perindopril [20-22]	Quinapril [2, 17-19]	Ramipril [23-26]	Trandolapril [15, 16]	Zofenopril [9, 10]
Gastrointestinal inflammation					✓		
Headache	✓	✓	✓	✓	✓	✓	✓
Hyperkalaemia	✓			✓	✓		
Hypersensitivity/ angioneurotic oedema	✓						
Increases in serum creatinine	✓			✓			
Insomnia				✓			
Muscle cramps			✓		✓		
Myalgia				✓	✓		
Nausea	✓			✓	✓		✓
Orthostatic symptoms (including hypotension)	✓	✓	✓	✓	✓	✓	
Palpitations							
Paraesthesia			✓	✓			
Pharyngitis				✓			
Photosensitivity reaction							
Pollakiuria							
Pruritis			✓				
Rash	✓		✓		✓		
Renal dysfunction		✓					

Adverse drug reaction	Enalapril 11-14	Lisinopril 5-8	Perindopril 20-22	Quinapril 2, 17-19	Ramipril 23-26	Trandolapril 15, 16	Zofenopril 9, 10
Rhinitis				✓			
Rhythm disturbances	✓						
Sinusitis					✓		
Symptoms of upper respiratory tract infection							
Syncope	✓				✓		
Tachycardia	✓						
Taste alteration	✓						
Tinnitus			✓				
Vertigo			✓				
Vomiting		✓		✓	✓		✓

As outlined in table 6, enalapril and quinapril have the greatest number of common ADRs reported in its SmPC. Conversely, trandolapril, zofenopril and lisinopril appear to have the best safety profile based on the number of common ADRs reported in its SmPC. Of the ACE inhibitors that are licensed in both hypertension and heart failure, lisinopril and trandolapril appear to have the most favourable safety profile, based on the number of common ADRs reported in its SmPC.

Lisinopril, trandolapril and zofenopril are the preferred ACE inhibitors in terms of an adverse drug reactions profile.

5.5 Contraindications & cautions

Prescribers are required to regularly monitor patients in whom caution is advised when prescribing an ACE inhibitor and to avoid prescribing ACE inhibitors where they are deemed contraindicated. It is advisable to consult the SmPC of the individual ACE inhibitors for guidance on contraindications and cautions, available at www.hpra.ie.

5.5.1 Contraindications

- **Angioedema:** All ACE inhibitors are contraindicated in patients with a history of angioedema associated with previous ACE inhibitor treatment. Enalapril, lisinopril, perindopril, quinapril, ramipril and trandolapril are contraindicated in patients with hereditary or idiopathic angioedema.[2, 5-26]

- The **concomitant use of ACE inhibitors with aliskiren-containing products** is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate < 60 ml/min/1.73 m²).[2, 5-26]

- The **concomitant use of ACE inhibitors with sacubitril/valsartan** therapy is contraindicated. ACE inhibitors must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.[2, 5-26]

- **Hypersensitivity:** All ACE inhibitors are contraindicated where there is hypersensitivity to the active substance, related compounds or any of the excipients. All ACE inhibitors reviewed, except lisinopril and ramipril, contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take medicines containing lactose.[2, 5-26]

- **Pregnancy:** The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors during the second and third trimesters of pregnancy is contraindicated, as it has been associated with foetal and neonatal damage.[2, 5-26]

5.5.2 Cautions

- **Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS):** There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). If dual blockade of the RAAS is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and BP. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. [2, 5-26, 36]

  The combination of ACE inhibitor/ARB for heart failure with reduced ejection fraction was reviewed by the European Medicines Agency (EMA), which suggested that benefits are thought to outweigh risks only in a select group of patients with heart failure with reduced ejection fraction in whom other treatments are unsuitable.[43]

- **Ethnic differences**: ACE inhibitors are apparently less effective in lowering BP in people of black African/African-Caribbean family origin than in people of non-black African/African-Caribbean family origin, possibly because of a higher prevalence of low-renin states in the black African/African-Caribbean hypertensive population. The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black patients of African origin than in non-black patients.[2, 5-26]

- **Haemodialysis patients**: Caution is advised when undergoing certain treatments: Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g., polyacrylonitril membranes) and low-density lipoprotein apheresis with dextran sulfate due to increased risk of severe anaphylactoid reactions. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.[2, 5-26]

- **Hyperkalaemia:** Concomitant use of ACE inhibitors with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicines that may increase potassium levels (e.g. heparin) may lead to increases in serum

potassium in hypertensive patients. In the elderly, in patients with renal insufficiency, patients with diabetes and/or in patients with other co-morbidities, the risk of hyperkalaemia, which may be fatal, is increased. Monitoring of potassium should be undertaken as appropriate. [2, 5-26, 36]

- **Impaired liver function**: Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Close monitoring is required.[2, 5-26]

- **Mitral valve stenosis:** ACE inhibitors should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy, due to the risk of hypotension.[2, 5-26]

- **Neutropenia/agranulocytosis**: ACE inhibitors have been rarely associated with agranulocytosis and bone marrow depression in patients with uncomplicated hypertension but more frequently in patients with renal impairment, especially if they also have collagen vascular disease. Monitoring of white blood cell counts in patients with collagen vascular disease and/or renal diseases should be considered.[2, 5-26]

- **Primary aldosteronism:** Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of ACE inhibitors is not recommended.[2, 5-26]

- **Renal impairment:** ACE inhibitors should be used in caution in those with pre-existing renovascular disease, and should be initiated by a specialist only. Hyperkalaemia and other adverse effects are more common, and the dose may need to be reduced. [2, 5-26, 36]

There are no significant differences between ACE inhibitors in terms of contraindications and cautions.

5.6 Drug interactions

An overview of potential drug-drug interactions that may occur with ACE inhibitors and commonly prescribed drugs in Ireland is summarised below. This list is not exhaustive and it is advisable to consult the SmPC of individual ACE inhibitors for a comprehensive list of drug interactions, available at www.hpra.ie.

- **Antidiabetic agents:** In rare cases, diabetic patients receiving an ACE inhibitor concomitantly with insulin or oral antidiabetics may develop hypoglycaemia. This phenomenon appears to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.[2, 5-26, 44]
- **Diuretics**: Patients on diuretics or fluid-depleted patients may occasionally experience an excessive reduction in BP when therapy with an ACE inhibitor is started.[2, 5-26, 44]
- **Drugs that block the Renin-Angiotensin System:** Clinical trial data has shown that the dual blockade of the RAAS through the combined use of ACE inhibitors, angiotensin-II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.[2, 5-26, 44]
- **Drugs that increase serum potassium concentration:** ACE inhibitors are capable of lowering aldosterone levels which may lead to hyperkalaemia in some patients treated with ACE inhibitors. Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care must be taken when ACE is co-administered with other agents that increase serum potassium, such as trimethoprim, cotrimoxazole, ciclosporin and heparin.[2, 5-26, 44]
- **Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.[2, 5-26, 44]
- **Hypotensive Agents:** Concomitant use of hypotensive agents may increase the hypotensive effects of ACE inhibitors. Such agents include, but are not limited to, treatment with nitroglycerine and other nitrates, some vasodilators, tricyclic antidepressants, antipsychotics, anaesthetics and narcotics.[2, 5-26, 44]

- **Lithium:** Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of ACE inhibitors with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.[2, 5-26, 44]
- **Medicines increasing the risk of angioedema:** The concomitant use of ACE inhibitors with the sacubitril-valsartan combination is contraindicated as this increases the risk of angioedema. The sacubitril-valsartan combination must not be started until 36 hours after taking the last dose of ACE inhibitor. Concomitant use of ACE inhibitors with racecadotril, mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema.[2, 5-26, 44]
- **Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid used as an anti-inflammatory agent:** When ACE inhibitors are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.[2, 5-26, 44]

There are no significant differences between ACE inhibitors in terms of drug interaction profiles.

5.7 Patient factors

In the absence of clinical outcome data demonstrating superiority of one drug over another, drugs taken once daily are preferred to those requiring multiple daily doses.

Lisinopril, perindopril and trandolapril are licensed for once-daily dosing for both hypertension and heart failure.[5-8, 15-16, 20-22] Ramipril is usually administered once daily for hypertension but two administrations per day are preferable in heart failure.[23-26] Similarly, enalapril is licensed for once-daily dosing for hypertension and once or twice-daily dosing for heart failure.[11-14] Quinapril is licensed for once or twice-daily dosing in both hypertension and heart failure.[2, 17-19] Zofenopril may be taken once twice daily for hypertension.[9, 10]

Lisinopril, perindopril and trandolapril are favourable in terms of dosing administration in the treatment of hypertension and heart failure.

5.8 Cost

Value for money is a consideration when choosing a preferred ACE inhibitor. It is also a consideration for patients who pay for their medicines. A drug of lower acquisition cost is preferred unless the more expensive drug has a proven advantage in terms of either efficacy or safety.

Figure 3 below illustrates the PCRS reimbursed cost comparison of 28 dosage units of each ACE inhibitor. The most expensive ACE inhibitor is quinapril 40 mg. The least expensive ACE inhibitor is ramipril 2.5 mg. Of note, enalapril 2.5 mg is more expensive than enalapril 5 mg (€3.91 versus €3.84), quinapril 10 mg is more expensive than quinapril 20 mg (€7.13 versus €6.42), and ramipril 1.25 mg is more expensive than ramipril 2.5 mg (€2.10 versus €1.96). Prices are correct as of 11/02/2022.[45]

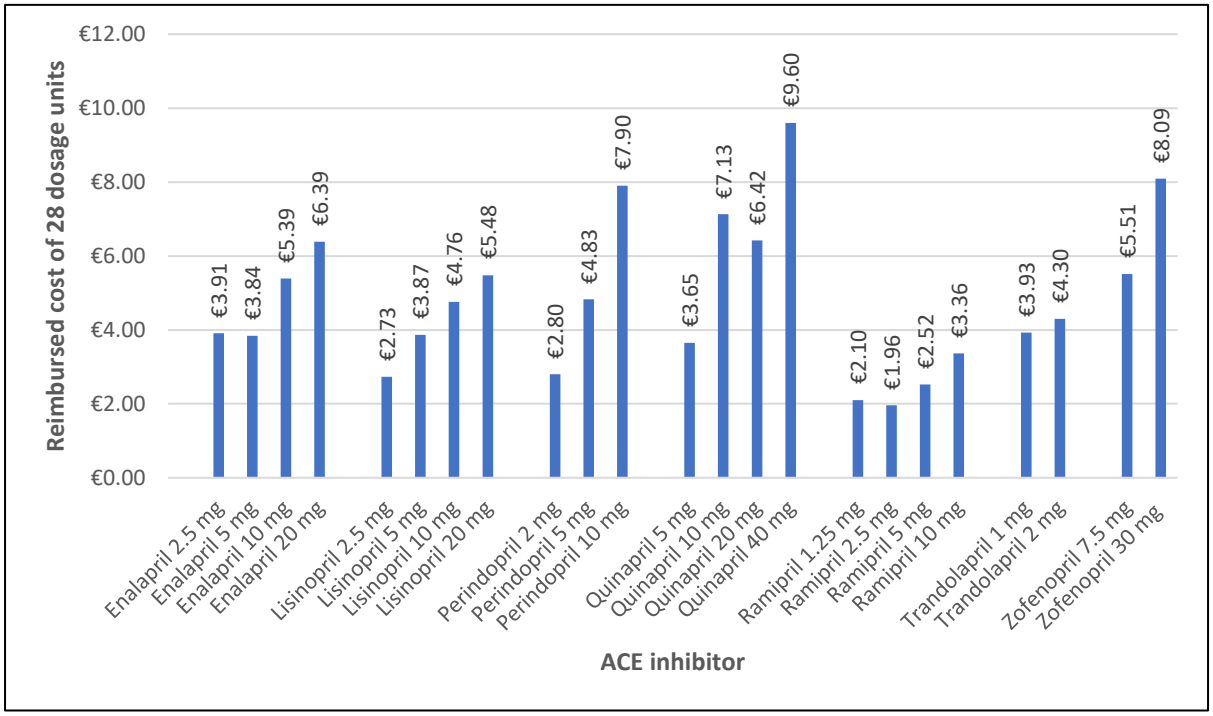

Figure 3: PCRS reimbursed cost of 28 dosage units of each ACE inhibitor

The World Health Organisation (WHO) collaborating centre for drug statistics methodology lists the defined daily dose (DDD) for each ACE inhibitor for the treatment of hypertension, and this is utilised to compare the reimbursed cost of each ACE inhibitor.[46]

Table 7: The defined daily dose (DDD) of each ACE inhibitor for the treatment of mild-moderate hypertension

ACE inhibitor	Oral DDD
Enalapril	10 mg
Lisinopril	10 mg
Perindopril	4 mg
Quinapril	15 mg
Ramipril	2.5 mg
Trandolapril	2 mg
Zofenopril	30 mg

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[46] The oral DDDs are based on the average doses needed to reduce the blood pressure to a normal level in patients with mild-moderate hypertension. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. The DDD can sometimes be a dose that is rarely or never prescribed because it is an average of two or more commonly used doses.[46]

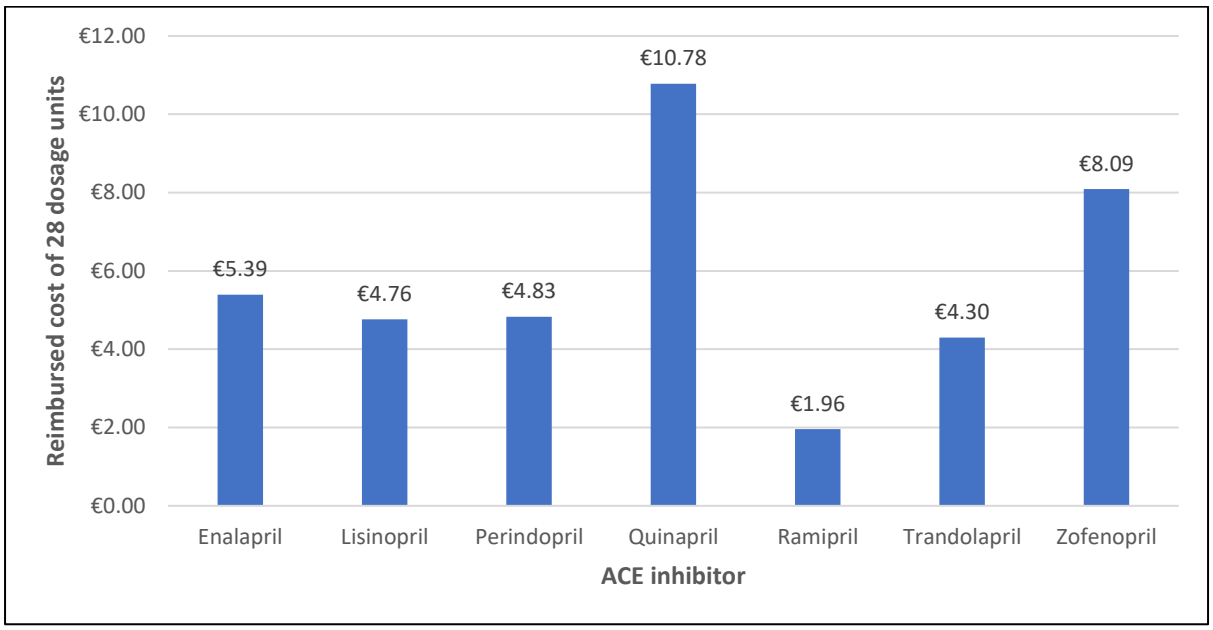

Figure 4: PCRS reimbursed cost of 28 dosage units based on defined daily dose

Figure 4 illustrates a comparison of the ACE inhibitor's reimbursed cost of 28 dosage units, based on DDD. It shows that ramipril is the least expensive ACE inhibitor, while quinapril is the most expensive based on the DDD.

For the treatment of hypertension, ramipril dosing should be individualised according to the patient profile and BP control. Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily. The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose is 10 mg daily.[23-26]

For the treatment of heart failure, the recommended initial dose of ramipril is 1.25 mg daily in patients stabilised on diuretic therapy. The dose should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg.[23-26]

Ramipril is the preferred ACE inhibitor in terms of cost in the treatment of hypertension and heart failure.

5.9 National prescribing trends

The MMP recognises that clinical experience is a factor for prescribers when choosing a medication. In order to determine prescribing trends for the ACE inhibitors under review, the MMP performed analyses of the PCRS pharmacy claims database.

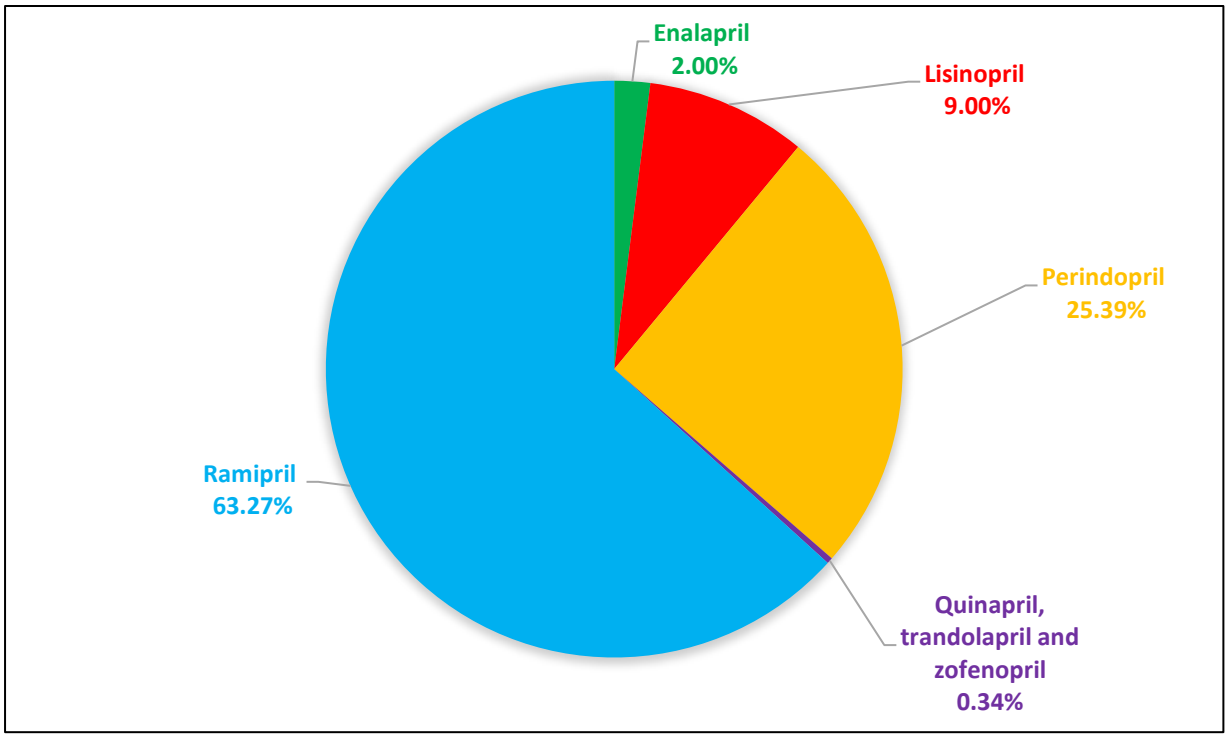

Figure 5: Distribution of the volume of claims reimbursed by PCRS for ACE inhibitors under the community drugs schemes in 2020

Figure 5 illustrates the distribution of the total volume of claims (i.e. number of prescriptions) subdivided by individual ACE inhibitors reimbursed by the PCRS on all CDS in 2020. Ramipril represents the majority of the volume of claims reimbursed, followed by perindopril, lisinopril and enalapril. Quinapril, trandolapril and zofenopril combined accounted for less than 1% of the volume of claims of ACE inhibitors reimbursed 2020.[4]

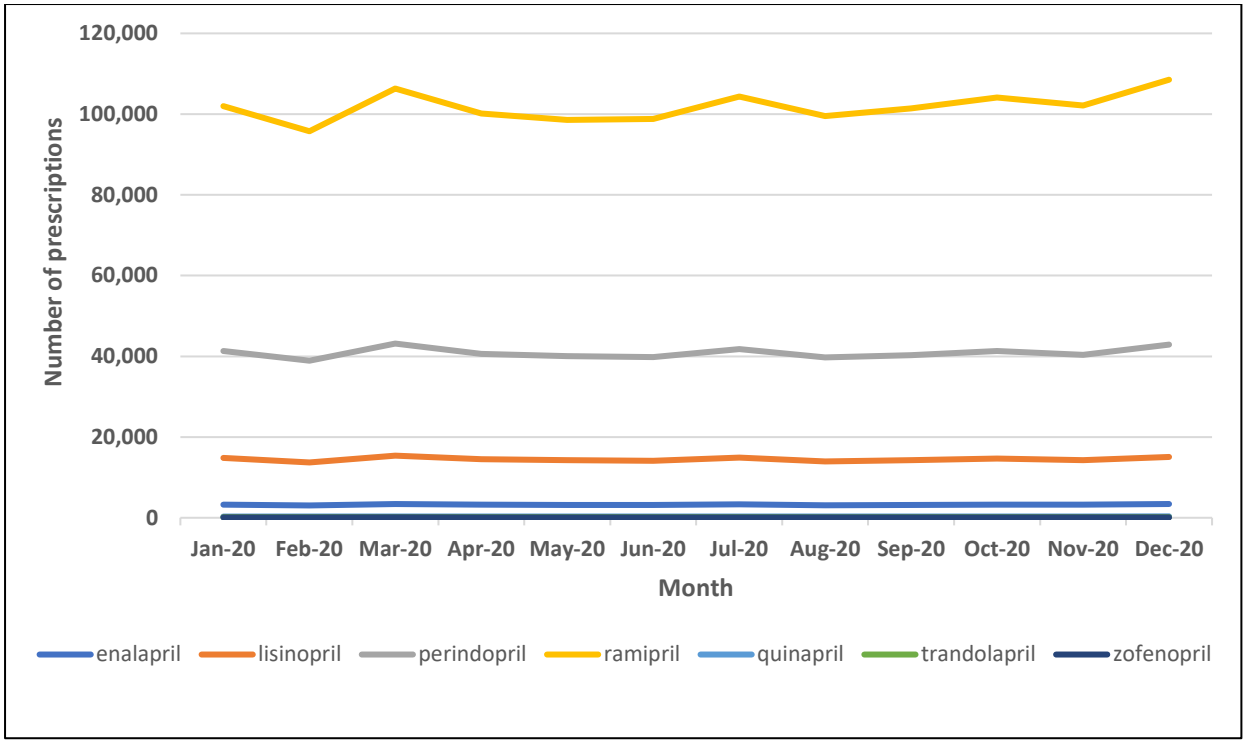

Figure 6: Number of prescriptions per month for ACE inhibitors reimbursed under community drug schemes in 2020

Figure 6 highlights that in the twelve month period from January 2020 to December 2020 inclusive, ramipril is the most commonly prescribed ACE inhibitor on all CDS; in January 2020 there were 101,964 prescriptions for ramipril increasing to 108,520 prescriptions in December 2020. There was limited fluctuation in the number of prescriptions for all other ACE inhibitors.[4]

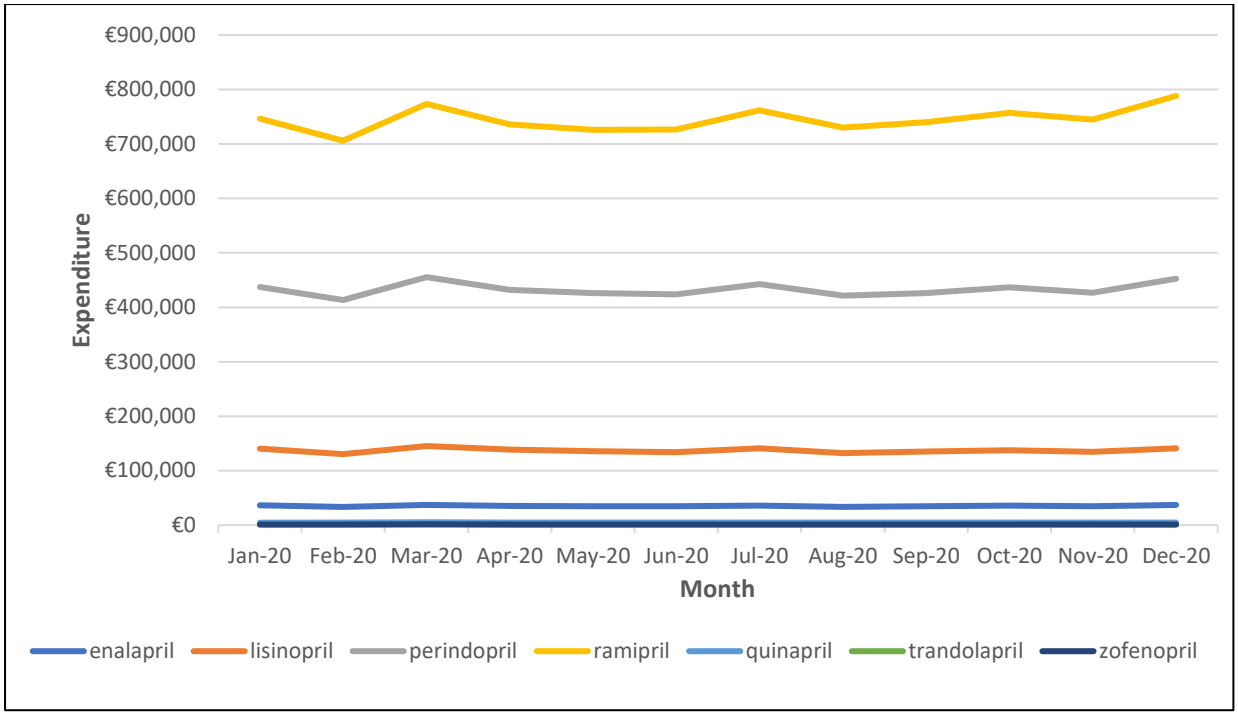

Figure 7: Total expenditure per month for each ACE inhibitor reimbursed under community drug schemes in 2020

Figure 7 illustrates that total monthly expenditure for ACE inhibitors in 2020 on all CDS followed a similar trend. Expenditure dipped in February 2020 but increased again from March 2020 where it steadied off. The highest expenditure was observed for ramipril followed by perindopril.[4]

Total annual expenditure on ACE inhibitors under the CDS accounted for €16.29 million in 2020. Within that, the largest expenditure was on ramipril (€8.94 million), followed by perindopril (€5.2 million), lisinopril (€1.65 million) and enalapril (€422,894). Quinapril, zofenopril and trandolapril each accounted for expenditure less than €100,000 in 2020.[4]

Table 8: Breakdown of the total number of prescriptions for different strengths of ACE inhibitors on the community drug schemes from January 2020 to December 2020

ACE inhibitor	Number of prescriptions*	Percentage of prescriptions
Enalapril 2.5 mg	3,100	8.01%
Enalapril 5 mg	11,533	29.79%
Enalapril 10 mg	12,871	33.25%
Enalapril 20 mg	11,208	28.95%
Total	**38,712**	
Lisinopril 2.5 mg	18,304	10.53%
Lisinopril 5 mg	45,923	26.42%
Lisinopril 10 mg	61,605	35.44%
Lisinopril 20 mg	48,002	27.61%
Total	**173,834**	
Perindopril 2 mg	13,503	2.76%
Perindopril 4 mg	17,056	3.48%
Perindopril 5 mg	297,669	60.72%
Perindopril 8 mg	7,406	1.51%
Perindopril 10 mg	154,583	31.53%
Total	**490,217**	
Quinapril 5 mg	380	9.86%
Quinapril 10 mg	2,087	54.15%
Quinapril 20 mg	579	15.02%
Quinapril 40 mg	808	20.97%
Total	**3,854**	
Ramipril 1.25 mg	177,961	14.57%
Ramipril 2.5 mg	377,617	30.91%
Ramipril 5 mg	372,850	30.52%
Ramipril 10 mg	293,265	24%
Total	**1,221,693**	
Trandolapril 1 mg	350	23.38%
Trandolapril 2 mg	1,147	76.62%
Total	**1,497**	
Zofenopril 7.5 mg	88	7.5%
Zofenopril 30 mg	1,086	92.5%
Total	**1,174**	

*Cumulative number of prescriptions over the twelve month period.

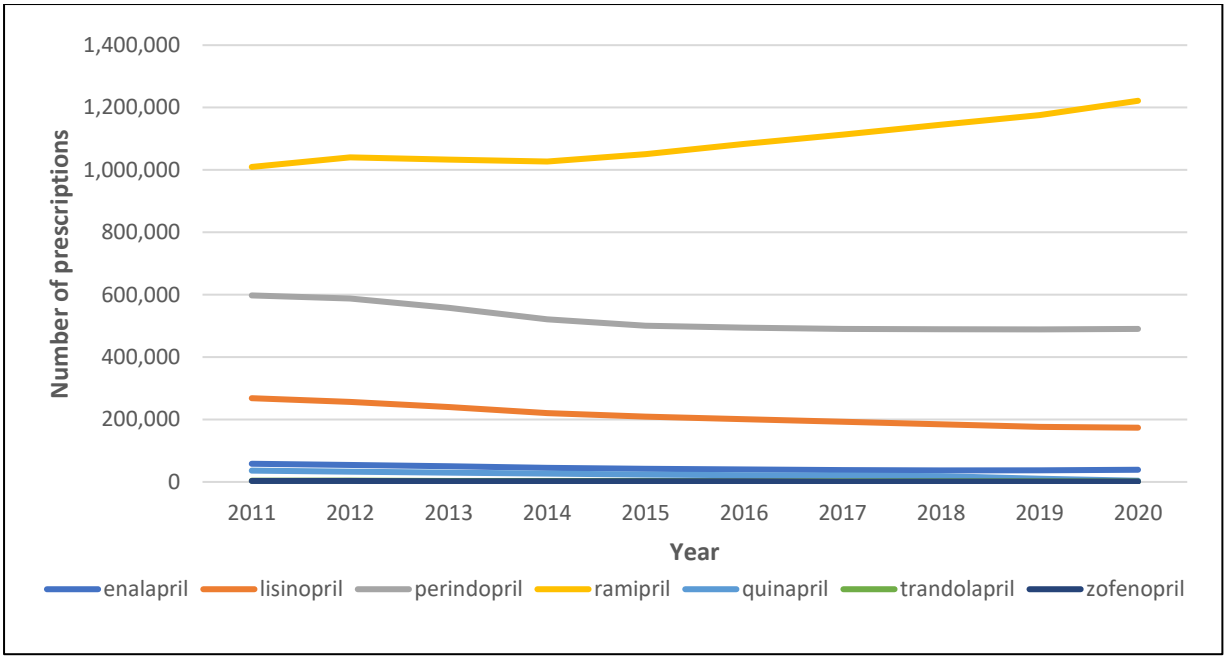

Figure 8: Total annual number of prescriptions for each ACE inhibitor reimbursed under community drug schemes 2011 – 2020

Figure 8 illustrates that ramipril had the highest number of prescriptions from 2011 – 2020.[4] The MMP recommended ramipril as the preferred ACE inhibitor in September 2013.[1] From 2014 onwards, following the MMP's recommendation, the number of prescriptions for ramipril has increased each year. The ACE inhibitors with the next largest volume of prescriptions are perindopril and lisinopril; there has been a decline in the number of prescriptions for both of these medicines since 2014.

Ramipril accounts for the greatest share of the ACE inhibitors on the community drug schemes. There has been an increase in the prescribing of ramipril since the MMP recommendation in 2013.

6. Conclusion

Following a review of the available evidence and taking into account the following criteria: licensed therapeutic indications, clinical outcome data, national and international clinical guidelines, drug interactions profiles, patient factors, cost and national prescribing trends, ramipril is recommended by the MMP as the preferred ACE inhibitor for the treatment of hypertension and heart failure.

Based on the current evidence, ramipril is the MMP's preferred ACE inhibitor for the treatment of hypertension and heart failure.

- ✓ **Ramipril is licensed for the treatment of hypertension and heart failure.**
- ✓ **Ramipril has a favourable adverse drug reaction profile.**
- ✓ **Ramipril has a favourable drug interaction profile.**
- ✓ **Ramipril has a favourable cost profile across all available strengths.**

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