Medicines Management Programme

Preferred Drugs

Angiotensin-II Receptor Blockers

(ARBs)

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List of abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACE2	Angiotensin-converting enzyme 2
ADR	Adverse drug reaction
AHA	American Heart Association
ARB	Angiotensin-II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
AT_1	Angiotensin type 1
BIHS	British and Irish Hypertension Society
BP	Blood pressure
CCB	Calcium channel blocker
CDS	Community Drug Schemes
CHMP	Committee for Medicinal Products for Human Use
CYP	Cytochrome P450
DDD	Defined daily dose
DPS	Drugs Payment Scheme
EMA	European Medicines Agency
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GMS	General Medical Services
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
LTI	Long Term Illness
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid receptor antagonist
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PCRS	Primary Care Reimbursement Service
RAS	Renin-Angiotensin System
RAAS	Renin-Angiotensin-Aldosterone System
SGLT2	Sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

Acknowledgements

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1. Purpose

Candesartan has been the Health Service Executive-Medicines Management Programme (HSE-MMP) preferred angiotensin-II receptor blocker (ARB) since July 2014.[1] The purpose of this report is to review the choice of preferred ARB 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 this drug for a particular condition. In this case, the use of ARBs in the management of patients with cardiovascular conditions, in particular hypertension and heart failure is reviewed.

Prescribers are encouraged to make the preferred drug their drug of first choice, when initiating an ARB and when there is a need to change from one ARB to another in the treatment of hypertension and 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 Product Characteristics (SmPC) to inform decisions made concerning individual patients.

2. Definitions

For the purpose of this report, the associated ingredient cost refers to the reimbursed cost of the named ARB as listed on the HSE-Primary Care Reimbursement Service (PCRS) website (www.pcrs.ie). Reimbursed ARBs licensed for the treatment of hypertension and 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 with all the relevant indications has been selected for the evaluation. Costs are correct as of 2nd February 2022.

3. Angiotensin-II receptor blockers

Renin-angiotensin system (RAS) blockers consist of ARBs, angiotensin-converting enzyme (ACE) inhibitors and direct renin inhibitors. They act by blocking or inhibiting the RAS. ARBs inhibit the actions of angiotensin II through selective binding of angiotensin type 1 (AT_1) receptors in vascular smooth muscle.[2] ARBs do not inhibit ACE, the enzyme which also degrades bradykinin. Therefore, ARBs are not expected to potentiate bradykinin-mediated adverse effects, as may be seen with ACE inhibitors, such as a persistent dry cough.[3]

There are eight ARBs licensed and reimbursed in Ireland under the CDS; azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan.[4,5]

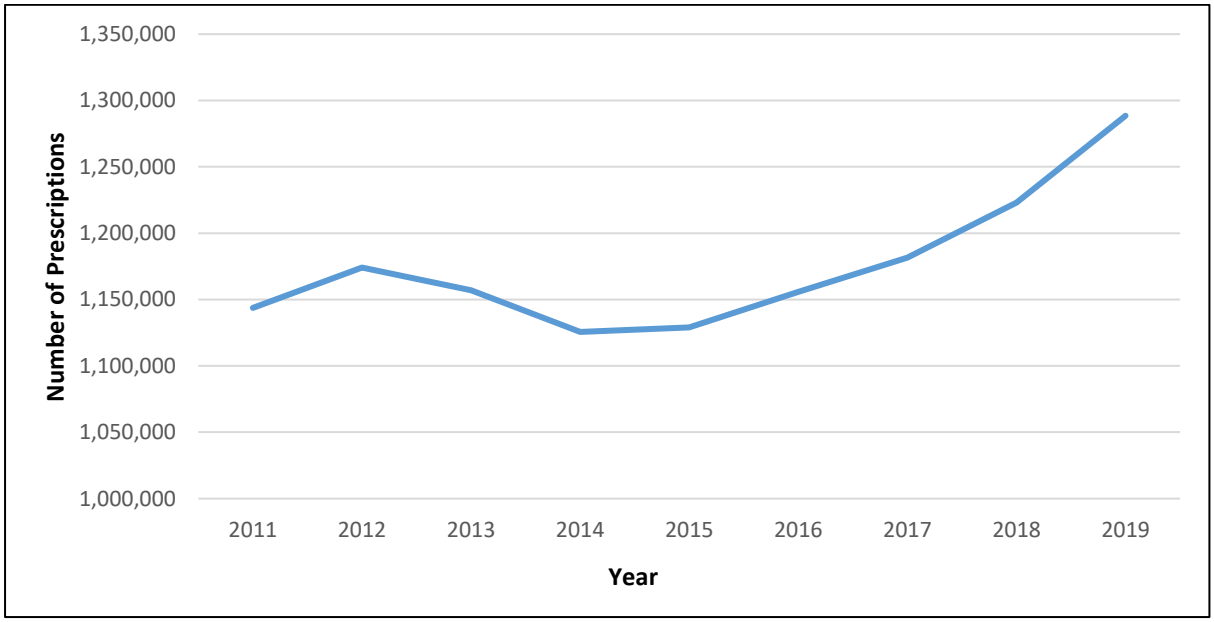

Figure 1: Combined total number of prescriptions for ARBs on all community drug schemes 2011-2019

Figure 1 illustrates the changes in the number of prescriptions for ARBs under the CDS from 2011 to 2019; there was an increase in the number of prescriptions from 2011-2012, followed by a decrease from 2012 to 2014. The number of prescriptions stabilised between 2014 and 2015, followed by a period of faster growth from 2015 to 2019.[6]

Total expenditure (inclusive of ingredient cost and pharmacy dispensing fees) in 2019 on ARBs under the CDS was €13.65 million.[6]

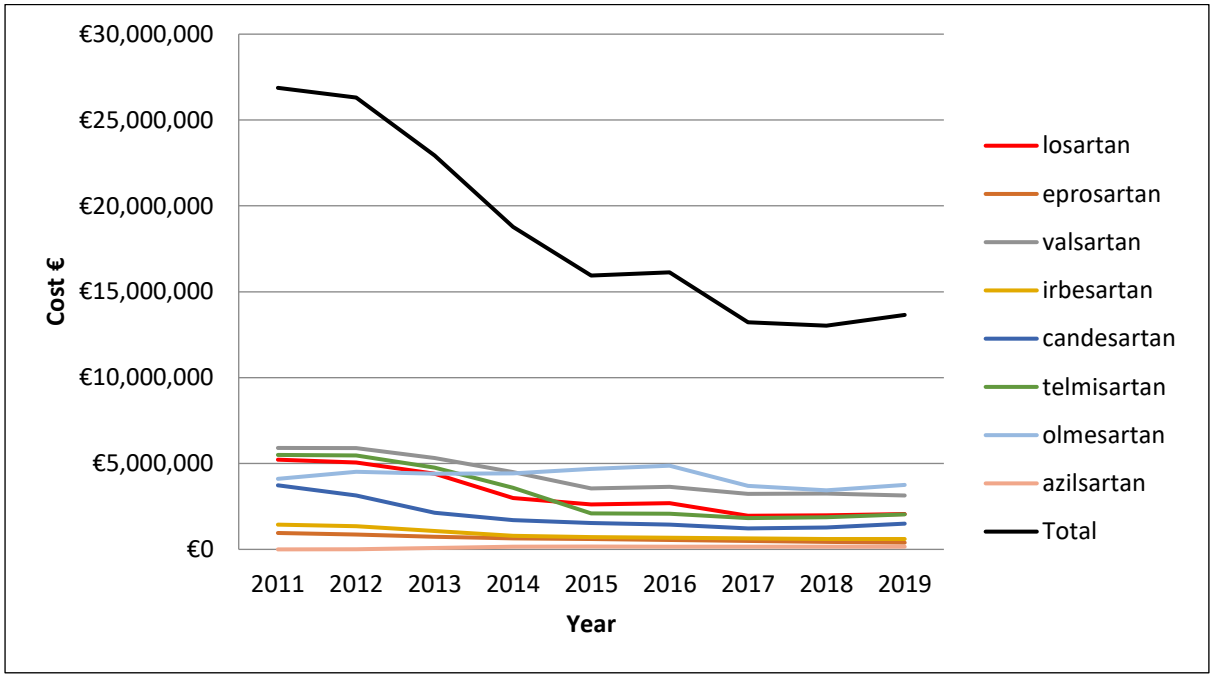

Figure 2: Total expenditure for ARBs on all community drug schemes 2011-2019

Figure 2 illustrates the sharp decline in total expenditure for ARBs under the CDS from 2011 (€26.87 million) to 2019 (€13.65 million). Total expenditure on ARBs has decreased following the introduction of generic substitution in 2013 and reference pricing of ARBs from 2014 onwards.[6]

4. Preferred angiotensin-II receptor blocker

Based on the current evidence, candesartan is the MMP's preferred ARB.

5. Selection criteria

A number of key criteria were considered in the MMP preferred ARB 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 licence 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 ARBs in hypertension and heart failure, the preferred ARB should be licensed at a minimum for these two indications.

All eight ARBs are licensed for the treatment of hypertension.[7-24] Three ARBs, candesartan, losartan and valsartan, are also indicated in heart failure.[8-10,14-16,21-24] Irbesartan and losartan are licensed for the treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive medicinal product regimen.[13-16] Losartan is also licensed for the reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by electrocardiogram.[14-16] Telmisartan is licensed for the reduction of cardiovascular morbidity in adults with a history of coronary heart disease, stroke or peripheral arterial disease or type 2 diabetes mellitus with documented target organ damage.[20] Valsartan is licensed in the treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.[21-24]

Losartan has the broadest range of licensed indications of all the ARBs included in this review. These differences in the licensing particulars were considered important in enabling a recommendation for a single preferred drug for ARBs. The licensed indications for ARBs are summarised in Table 1.

Table 1: Licensed therapeutic indications and frequency of administration for ARBs

Drug	Hypertension	Heart failure	Renal disease (diabetes)	Recent myocardial infarction	Reduction of stroke risk in left ventricular hypertrophy	Cardiovascular prevention	Frequency of administration
Azilsartan[7]	✓						Once Daily
Candesartan[8-10]	✓	✓					Once Daily
Eprosartan[11,12]	✓						Once Daily
Irbesartan[13]	✓		✓				Once Daily
Losartan[14-16]	✓	✓	✓		✓		Once Daily
Olmesartan[17-19]	✓						Once Daily
Telmisartan[20]	✓					✓	Once Daily
Valsartan[21-24]	✓	✓		✓			HTN: Once Daily HF/MI: Twice Daily

HF: Heart failure; HTN: Hypertension; MI: Myocardial infarction

All licensed ARBs are indicated for the treatment of hypertension. Candesartan, losartan and valsartan are also licensed in heart failure. Losartan has the broadest range of licensed indications of all the ARBs.

5.1.1 Hypertension

Hypertension is defined as persistently raised arterial blood pressure (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.[3]

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% to 45%. It is estimated that the number of people with hypertension will increase by 15% to 20% by 2025, reaching close to 1.5 billion.[25]

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.[3,26]

The risk of heart failure is greater in men, smokers and people with diabetes, and increases with age.[3]

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.[3]

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.[26]

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%.[26]

Patients with a left ventricular ejection fraction (LVEF) 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.[26]

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.[26]

5.2 Clinical outcome data

When the HSE-MMP initial review of ARBs was undertaken in 2014, consideration was given to pivotal clinical trials and clinical evidence available at that time.[1] This review evaluates updated evidence since the publication of the 2014 version of the preferred drug document for ARBs. No new clinical trials were identified for ARBs in the treatment of hypertension and/or 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 and observational studies, provide a means of assessing the general and comparative efficacy of ARBs, and were considered as part of the review process.

- An observational study by Mazza et al. (2017) involving 114 hypertensive patients aimed to evaluate the costs/health benefit and effectiveness of treatment with ARBs in uncomplicated essential hypertension. This retrospective, cross-sectional study was conducted on hypertensive patients without a history of cardiovascular events by using pharmacy dispensing records. The BP-lowering effects of candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan were evaluated.[27]

  The BP-lowering effect of ARBs both in monotherapy and in fixed-dose combination with hydrochlorothiazide, at the doses commonly used in practice to reach BP control (i.e. BP < 140/90 mmHg), was analysed and evaluated after an average of six-months follow-up. Results showed that olmesartan (32.4%) was the most frequently prescribed drug followed by valsartan (18.3%) with no statistical differences between genders in each group. Treatment with candesartan (14.1%) and olmesartan (32.4%) versus other ARBs resulted in a significant decrease in BP-lowering effect when used as monotherapy. There was no significant difference in BP-lowering effect between ARBs when used in fixed-dose combination with hydrochlorothiazide. In this study, candesartan was estimated to be the most favourable treatment option of the ARBs tested.[27]

  Limitations to this study include that it is monocentric, retrospective and limited by its short treatment period and relatively small-sized treatment groups. The BP-lowering effects of ARBs were evaluated using office BP measurement which is less accurate than 24-hour ambulatory BP monitoring. The researchers could not assess the adherence to treatment of the hypertensive patients.[27]

- A network meta-analysis by Tsoi et al. (2018) was conducted to determine the comparative efficacy of different ARBs with respect to outcomes of BP reduction (at

24 and 52 weeks) and the prevention of cardiovascular disease (> 104 weeks). This involved 36 studies representing 28 unique trials.[2]

BP reduction, based on 12 studies (n = 807 patients), with a fixed-dose regimen was found to be similar amongst ARBs at both 24 and 52 weeks. Treat-to-target was excluded from the analysis of BP as a specific BP target would have to have been pre-defined for all treatment arms within a trial. At 24 weeks, five members of the ARB class were studied in which only six of the 15 possible pair-wise comparisons were studied directly. Data at this point indicated no difference between members of the ARB class. At 52 weeks, only two members of the ARB class could be studied, losartan and telmisartan, sharing the common comparator of hydrochlorothiazide which is not relevant to this evaluation.[2]

A network meta-analysis of five studies (n = 16,716 patients) with a treat-to-target approach found that prevention of all-cause mortality, stroke and myocardial infarction was similar across the five ARBs evaluated - candesartan, irbesartan, losartan, olmesartan and telmisartan.[2]

The study concluded that there was no difference in the comparative efficacy between ARBs with respect to BP control or the incidence of cardiovascular events following long-term treatment. No individual ARB offered significantly greater protection from cardiovascular morbidity and mortality. These results summarise the experience so far from long-term clinical trials on this drug class by incorporating both direct and indirect comparisons, including those that have never been directly compared quantitatively in previous trials or reviews.[2]

Limitations include that safety outcomes were not investigated in this study and patient compliance and adherence to medication was not assessed.[2]

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

- A network meta-analysis by Luan et al. (2018) available in abstract form, involved 27 randomised controlled trials with 29 direct comparisons in patients with heart failure

treated with ARBs. The primary objective was to provide head-to-head comparisons between ARB drugs in terms of efficacy and safety. Six ARBs were included in this study; candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan.

Generally, losartan and telmisartan were significantly better than other ARBs in preventing all-cause mortality. Telmisartan ranked first for cardiovascular and non-cardiovascular mortality; it showed significant positive difference than irbesartan and candesartan for cardiovascular mortality and was significantly better than candesartan and valsartan for non-cardiovascular mortality. Although it is important to note that telmisartan is not licensed in heart failure. In terms of safety outcomes, there was no significant difference among ARB drugs.[28]

Limitations to this study include that it is only available in abstract form. Information is limited as to how the network meta-analysis was undertaken and results analysed.[28]

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

There were no significant differences in clinical efficacy noted among various ARBs 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 ARB
Irish College of General Practitioners[29]	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[30]	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[25]	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[31]	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[32]	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 guidance for the treatment of hypertension

Review body	Year	Initial drug treatment option	Preferred ARB
Clarity's Diagnosis and Treatment Guidance	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: Candesartan, losartan or valsartan • Diabetes and hypertension: Candesartan, irbesartan, losartan or valsartan

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.[29]

This guideline does not recommend a particular ARB 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.

If an ACE inhibitor is not tolerated, for example because of cough, offer an ARB to treat hypertension.

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.[30]

The guidance does not recommend a particular ARB 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 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.[25]

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. ARBs are associated with significantly lower treatment discontinuation rates for adverse events than those of all other antihypertensive therapies, and similar to placebo.[25]

The guideline does not state a preferred ARB 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 ARB 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.[31]

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. [32]

The guideline does not recommend a preferred ARB 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*.[30] 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.[34]

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 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 ARB 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 candesartan, losartan or valsartan as preferred ARBs in patients with hypertension and heart failure. In patients with diabetes and hypertension, candesartan, irbesartan, losartan or valsartan are recommended as preferred ARBs.[33]

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 criteria for selection of first-line antihypertensive agents, as the data is not conclusive.

Clinical guidelines do not identify a preferred ARB 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 ARB
Irish College of General Practitioners[35]	Heart failure in general practice	2019	• ACE inhibitor* + beta-blocker	None
National Institute for Health and Care Excellence[36]	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[37]	Management of heart failure	2017	• ACE inhibitor/ARB/ARNI + beta-blocker • Diuretics as needed	Candesartan, losartan or valsartan
European Society of Cardiology[26]	Acute and chronic heart failure	2021	• ACE inhibitor/ARNI** + beta-blocker + MRA + dapagliflozin/empagliflozin	Candesartan or valsartan

*An ARB is recommended if an ACE inhibitor is not tolerated; ** An ARB is recommended if an ACE inhibitor or an ARNI are not tolerated
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 guidance for the treatment of heart failure

Review body	Year	Initial drug treatment option	Preferred ARB
Clarity's Diagnosis and Treatment Guidance[38]	2017	• To relieve symptoms of fluid overload, a diuretic should be prescribed. • An ACE inhibitor* + beta-blocker should be prescribed to reduce morbidity and mortality, one drug at a time to ensure patient is stable.	Candesartan, losartan or valsartan

*An ARB is recommended if an ACE inhibitor is not tolerated
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.

ARBs are recommended only as an alternative in patients intolerant of an ACE inhibitor.[35]

This guideline does not recommend a particular ARB to use in the treatment of heart failure.

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. An ARB licensed for heart failure can be considered as an alternative to an ACE inhibitor for people who have heart failure with reduced ejection fraction and intolerable side-effects with ACE inhibitors.

The guidance recommends measuring serum sodium and potassium, and to assess renal function, before and after starting an ARB and after each dose increment. Once the target or maximum tolerated dose of an ARB is reached, the guidance recommends that treatment should be monitored monthly for three months and then at least every six months, and at any time the person becomes acutely unwell.[36]

This guidance does not recommend a particular ARB 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 2013 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 inhibitors (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.

The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic heart failure with reduced ejection fraction who are intolerant to ACE inhibitors because of cough or angioedema. Patients already tolerating ARBs for other indications may be continued on ARBs if they subsequently develop heart failure. ARBs should be started at low doses and titrated upward, with an attempt to use the doses that have been shown to reduce the risk of cardiovascular events in clinical trials.

This guideline specifies three licensed ARBs for the treatment of heart failure; candesartan, losartan and valsartan. However, it does not recommend a particular ARB from these three options to use in the treatment of heart failure.[37]

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.[26]

The guideline states that an ARB is recommended to reduce the risk of heart failure hospitalisations and cardiovascular deaths in symptomatic patients unable to tolerate an ACE inhibitor or an ARNI. The guideline outlines that candesartan has been shown to reduce cardiovascular deaths and heart failure hospitalisations in patients who were not receiving an ACE inhibitor due to previous intolerance. The guideline also outlines that valsartan, in

[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.[39]

addition to usual therapy, including an ACE inhibitor, has demonstrated a reduction in hospitalisations for heart failure.[26]

Candesartan and valsartan were included for the benefits they have shown in patients with heart failure but the guideline did not recommend a particular ARB.[26]

Clarity's Diagnosis and Treatment Guidance

Clarity's Diagnosis and Treatment Guidance state that the initial treatment option for heart failure is an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta-blocker should be prescribed to reduce morbidity and mortality, one drug at a time to ensure the patient is stable.

The guidance recommends candesartan, losartan or valsartan as preferred ARBs in patients with heart failure.[38]

Clinical guidelines do not specify a single preferred ARB for the treatment of heart failure however some identify candesartan, losartan and valsartan as appropriate ARB therapy.

5.4 Adverse drug reactions

The main adverse effects of ARBs include:

- **Renal impairment**: renal function should be monitored 1-2 weeks after starting an ARB, after each increase in dose, and regularly throughout treatment.[33]
- **Hyperkalaemia:** Serum electrolytes should be monitored 1-2 weeks after starting an ARB, after each increase in dose, and regularly throughout treatment.[33]
- **Angioedema:** ARBs can cause a non-allergic drug reaction which can precipitate angioedema. ARB treatment must be stopped immediately and consider starting an alternative drug treatment.[33]
- **Dizziness:** Dizziness due to hypotension occurs most commonly in people with intravascular volume depletion, such as those taking high-dose diuretics.[33]

The common adverse drug reactions (ADRs) [incidence of ≥ 1 in 100 to < 1 in 10] for individual ARBs 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.[7-24]

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

Adverse drug reaction	Azilsartan[7]	Candesartan [8-10]	Eprosartan [11,12]	Irbesartan[13]	Losartan[14-16]	Olmesartan[17-19]	Telmisartan[20]	Valsartan [21-24]
Dizziness	✓		✓	✓	✓	✓		✓
Diarrhoea	✓		✓	✓		✓		
Blood creatinine phosphokinase increased	✓					✓		
Infections and infestations		✓						
Nervous system disorders		✓						
Hyperkalaemia		✓		✓	✓			
Hypotension		✓						✓
Renal and urinary disorders		✓						
Headache			✓			✓		
Rhinitis			✓			✓		
Allergic skin reactions (e.g. rash, pruritus)			✓					
Nausea			✓	✓		✓		
Vomiting			✓	✓				
Asthenia			✓		✓			
Orthostatic dizziness				✓				✓
Orthostatic hypotension				✓	✓			✓
Musculoskeletal pain				✓		✓		
Fatigue				✓	✓	✓		
Blood creatinine kinase increased				✓				
Anaemia					✓			
Vertigo					✓			
Renal impairment					✓			✓
Renal failure					✓			✓

Adverse drug reaction	Azilsartan[7]	Candesartan [8-10]	Eprosartan [11,12]	Irbesartan[13]	Losartan[14-16]	Olmesartan[17-19]	Telmisartan[20]	Valsartan [21-24]
Blood urea, serum creatinine, and serum potassium increased					✓	✓		
Hypoglycaemia					✓			
Influenza-like symptoms						✓		
Hypertriglyceridaemia						✓		
Hyperuricaemia						✓		
Bronchitis						✓		
Pharyngitis						✓		
Cough						✓		
Gastroenteritis						✓		
Abdominal pain						✓		
Dyspepsia						✓		
Arthritis						✓		
Back pain						✓		
Haematuria						✓		
Urinary tract infection						✓		
Pain						✓		
Chest pain						✓		
Peripheral oedema						✓		
Hepatic enzymes increased						✓		

As outlined in Table 6, olmesartan has the greatest number of common ADRs reported in its SmPC. Conversely, telmisartan appears to have the best safety profile based on common ADRs reported in its SmPC. Of the three ARBs (candesartan, losartan and valsartan) that are licensed in both hypertension and heart failure, candesartan appears to have the most favourable safety profile, based on the number of common ADRs reported in its SmPC.

Telmisartan is the preferred ARB in terms of adverse drug reaction profiles. However, candesartan is the preferred ARB licensed in hypertension and heart failure.

5.5 Contraindications & cautions

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

5.5.1 Contraindications

- **Hypersensitivity**: All ARBs are contraindicated where there is hypersensitivity to the active substance or any of the excipients. Medicinal products containing ARBs, apart from azilsartan and valsartan, contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take ARBs.[7-24]

- **Pregnancy:** The use of ARBs is not recommended during the first trimester of pregnancy. The use of ARBs is contraindicated during the second and third trimesters of pregnancy as exposure to ARB therapy in the second and third trimester is known to induce human fetotoxicity and neonatal toxicity.[7-24,33]

- Concomitant use of an ARB with **aliskiren-containing products** is contraindicated in patients with diabetes mellitus or renal impairment (eGFR < 60 ml/min/1.73 m^2) due to an increased risk of adverse outcomes.[7-24,33]

- **Severe hepatic impairment, cholestasis or biliary obstructive disorders:** ARBs are contraindicated in patients with these disorders.[7-24]

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. [7-24,33,38]

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.[40]

Hyperkalaemia: Concomitant use of ARBs 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. [7-24,33,38]

Renal impairment: As with other agents inhibiting the RAAS, changes in renal function may be anticipated in susceptible patients treated with ARBs. Caution is recommended for use in patients with creatinine clearance < 30 ml/min or in patients undergoing dialysis.[3,7-24,33,38]

Renal artery stenosis: Medicines that affect the RAAS, including ARBs, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.[3,7-24,33,38]

Ethnic differences: ARBs and 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 higher prevalence of low-renin status in the black African/African-Caribbean hypertensive population.[3,7-24,33,38]

Aortic or mitral valve stenosis: As with other vasodilators, special caution is advised in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive cardiomyopathy.[3,7-24,33,38]

Hypotension and electrolyte/fluid imbalance: Symptomatic hypotension, especially after the first dose and after a dose increase, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of an ARB, or a lower starting dose should be used. [3,7-24,33,38]

Patients with **primary hyperaldosteronism** will not generally respond to antihypertensive medicines acting through inhibition of the RAAS. [3,7-24,33,38]

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

5.6 Drug interactions

The metabolism and interactions of ARBs are very much limited to the role of the cytochrome (CYP) 450 enzymes. It has been demonstrated that pharmacokinetic interactions of losartan with other agents are mainly via CYP2C9- and CYP3A4-mediated enzymes. The role played by CYP enzyme system in the metabolism of valsartan, candesartan, irbesartan, and azilsartan appears modest, and the CYP450 system has no influence on the metabolism of telmisartan, eprosartan and olmesartan.[41]

An overview of potential drug-drug interactions that may occur with ARBs and commonly prescribed drugs in Ireland is provided below. This list is not exhaustive and it is advisable to

consult the SmPC of individual ARBs for a comprehensive list of drug interactions, available at www.hpra.ie.

- **Lithium**: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of lithium and ACE inhibitors. A similar effect may occur with ARBs.[7-24]

- **Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels**: Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicines (e.g. heparin) may increase potassium levels. Monitoring of serum potassium should be undertaken as appropriate.[7-24]

- **Dual blockade of the RAAS, with ARBs, ACE inhibitors or aliskiren**: Clinical trial data has shown that it 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.[7-24,40]

- **Non-steroidal anti-inflammatory drugs (NSAIDs):** Attenuation of the antihypertensive effect may occur and there may be an increased risk of worsening of renal failure, including possible acute renal failure, and an increase in serum potassium, especially in people with poor pre-existing renal function and elderly people. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.[7-24]

ARBs, as a class, have consistently shown in clinical studies that their potential for interactions with other drugs is low in comparison with other classes of antihypertensive agents.[42]

There are no significant differences between ARBs in terms of drug interactions 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. As discussed in table 1, valsartan is administered twice daily in heart failure and once daily for hypertension.[21-24] Candesartan and losartan are taken once daily for both indications.[8-10, 14-16]

Candesartan and losartan are favourable in terms of dosing and administration in the treatment of hypertension and heart failure.

5.8 Cost

Value for money is a consideration when choosing a preferred ARB. 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 ARB. The most expensive ARB is azilsartan 80 mg. The least expensive ARB is losartan 50 mg. Of note is that candesartan 4 mg is more expensive than candesartan 8 mg (€3.63 versus €3.36), losartan 25 mg is more expensive than losartan 50 mg (€3.26 versus €2.80), telmisartan 20 mg is more expensive than telmisartan 40 mg (€4.48 versus €3.64), and valsartan 40 mg is more expensive than valsartan 80 mg (€4.20 versus €3.36). Prices are correct as of 02/02/2022.[4]

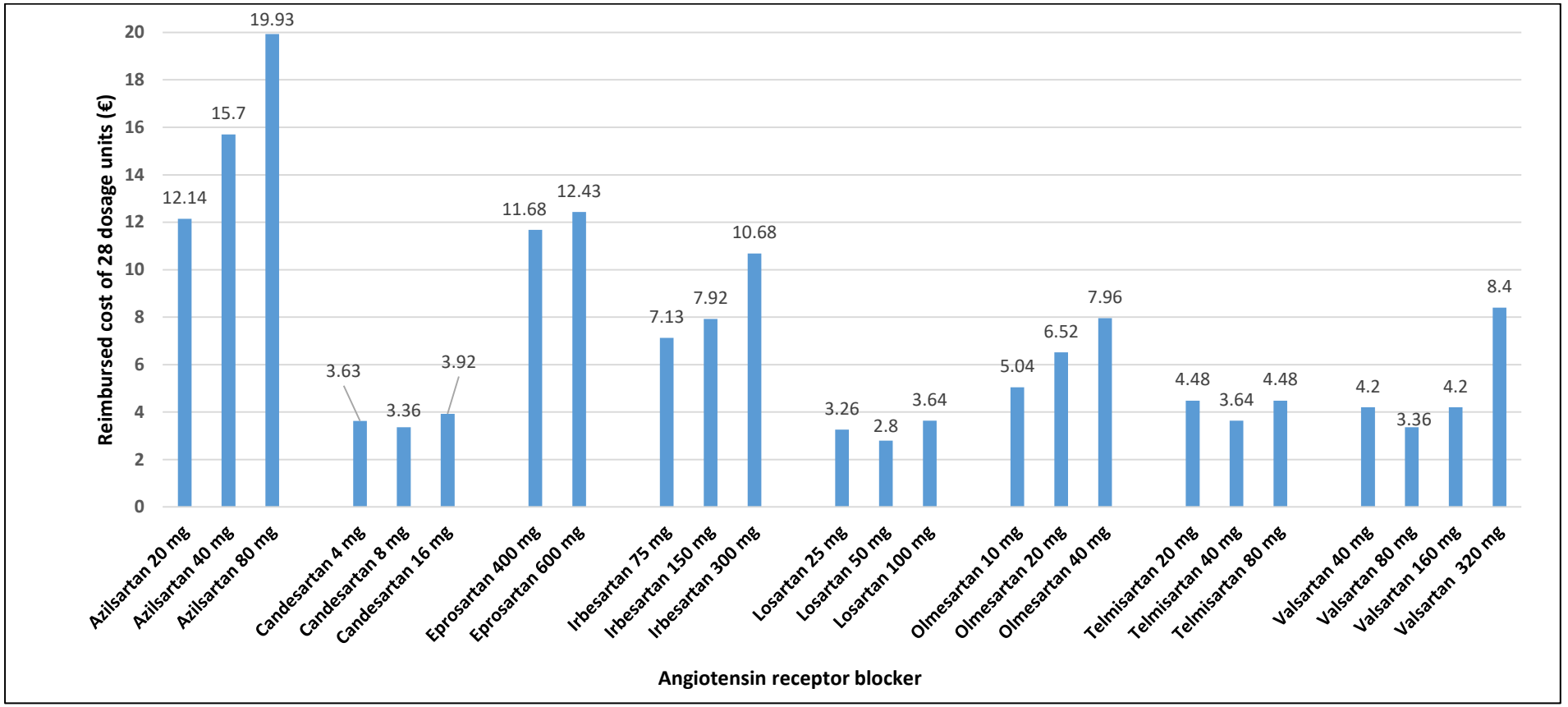

Figure 3: PCRS reimbursed cost of 28 dosage units of each ARB

The World Health Organisation (WHO) collaborating centre for drug statistics methodology lists the defined daily dose (DDD) for each ARB for the treatment of hypertension (Table 7), and this is utilised to compare the reimbursed cost of each ARB.[43]

Table 7: The defined daily dose of each ARB for the treatment of mild-moderate hypertension

ARB	DDD
Azilsartan	40 mg
Candesartan	8 mg
Eprosartan	600 mg
Irbesartan	150 mg
Losartan	50 mg
Olmesartan	20 mg
Telmisartan	40 mg
Valsartan	80 mg

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. 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.[43]

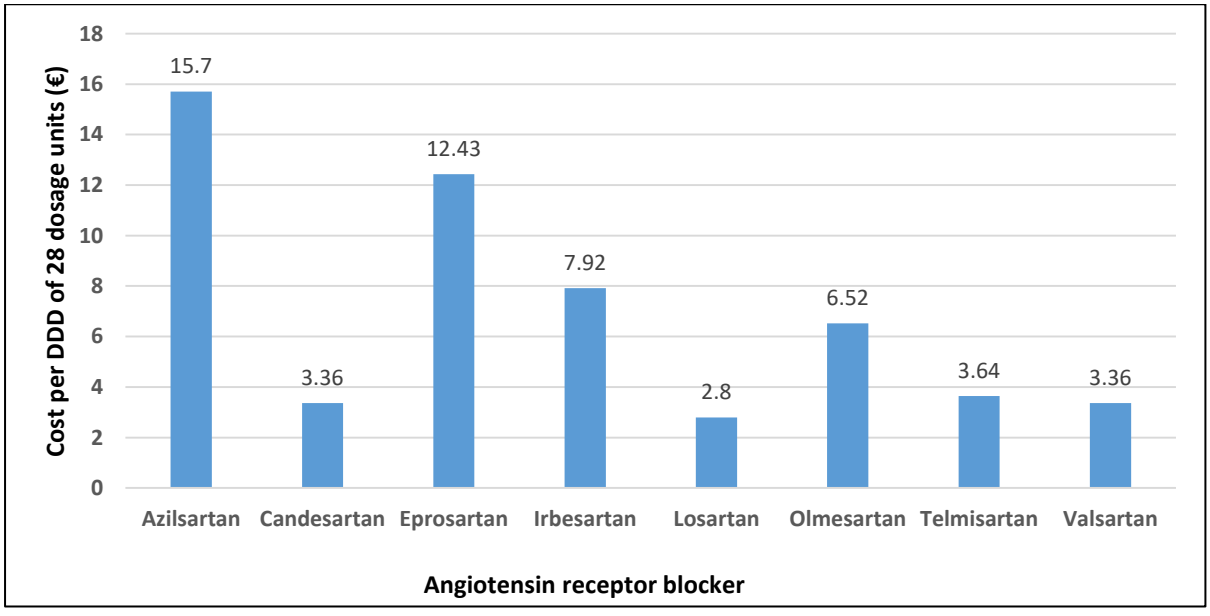

Figure 4: PCRS reimbursed cost of 28 dosage units based on defined daily dose

Figure 4 illustrates a cost comparison of the ARB's reimbursed cost of 28 dosage units, based on the DDD. It shows that losartan is the least expensive ARB, while azilsartan is the most expensive based on the DDD.

Based on DDD, the lowest cost ARBs are candesartan, losartan, telmisartan and valsartan. In hypertension, the recommended initial dose and usual maintenance dose of candesartan is 8 mg once daily. The dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. The recommended initial dose of candesartan in heart failure is 4 mg once daily that can be titrated up to the target dose of 32 mg once daily.

Treatment with losartan in hypertension is 50 mg once daily and can be increased to 100 mg once daily. Treatment with losartan in heart failure is 12.5 mg once daily and generally titrated at weekly intervals up to a maximum dose of 150 mg once daily.

Telmisartan 40 mg once daily is the usual effective dose for treatment of hypertension and can be increased to 80 mg once daily. Telmisartan, however, is not licensed in heart failure.

The recommended starting dose of valsartan in the treatment of hypertension is 80 mg once daily. The dose can be increased to 160 mg once daily and to a maximum of 320 mg once daily. For the treatment of heart failure, the recommended starting dose of valsartan is 40 mg twice daily and as tolerated by the patient can be titrated up to 80 mg and 160 mg twice daily. The cost of treatment with valsartan increases when treatment is increased to a daily dose of 320 mg, either administered once daily in the treatment of hypertension, or in divided doses for the treatment of heart failure.

Candesartan and losartan are the preferred ARBs in terms of cost in the treatment of hypertension and heart failure. Candesartan and losartan have a favourable cost profile across all strengths relative to other ARBs.

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 ARBs under review, the MMP performed analyses of the PCRS pharmacy claims database.

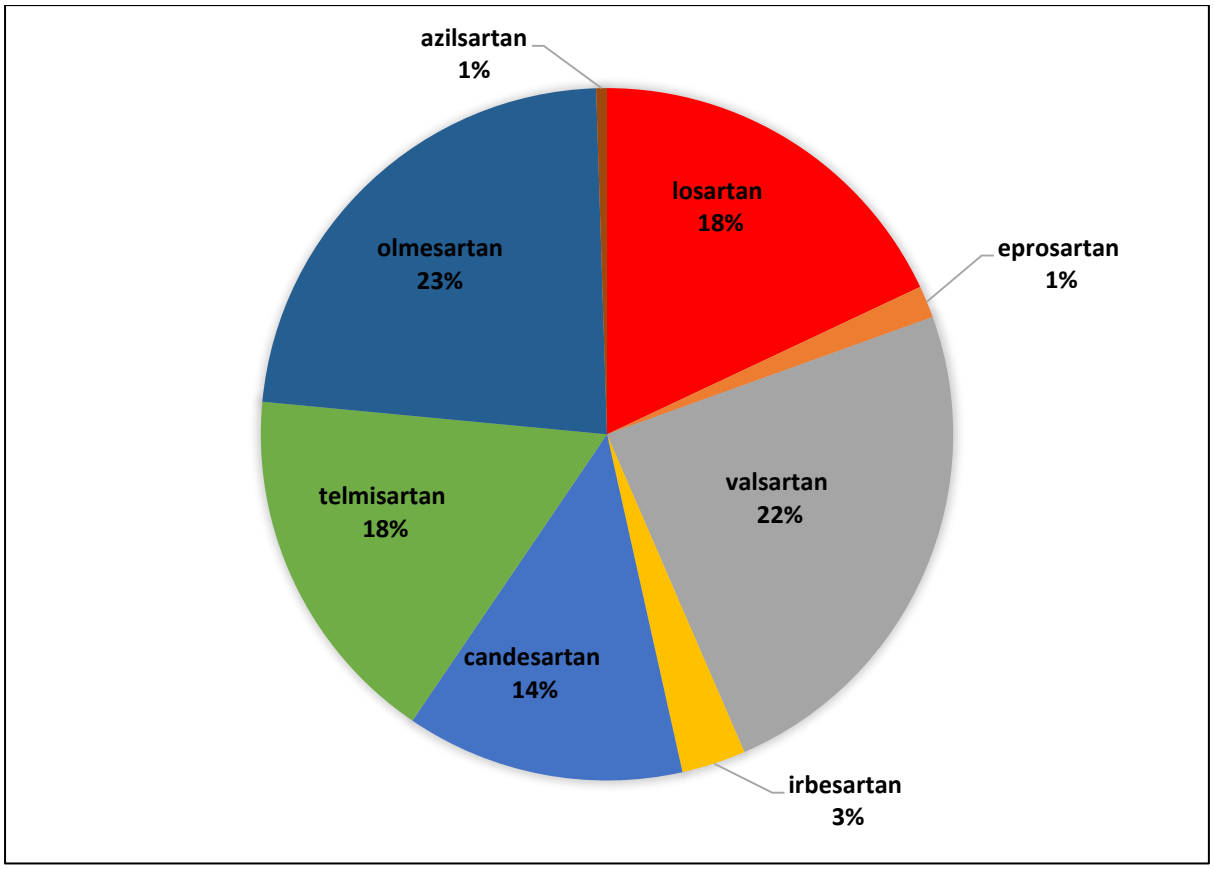

Figure 5: Distribution of the volume of claims reimbursed by the PCRS for ARBs on all community drug schemes July 2019 - June 2020

Figure 5 illustrates the distribution of the total volume of claims (i.e. number of prescriptions) subdivided by individual ARBs reimbursed by the PCRS on all CDS from July 2019 - June 2020. Olmesartan represents 23% of the volume of claims reimbursed, closely followed by valsartan at 22% and then losartan, telmisartan, candesartan, irbesartan, eprosartan and azilsartan.[6]

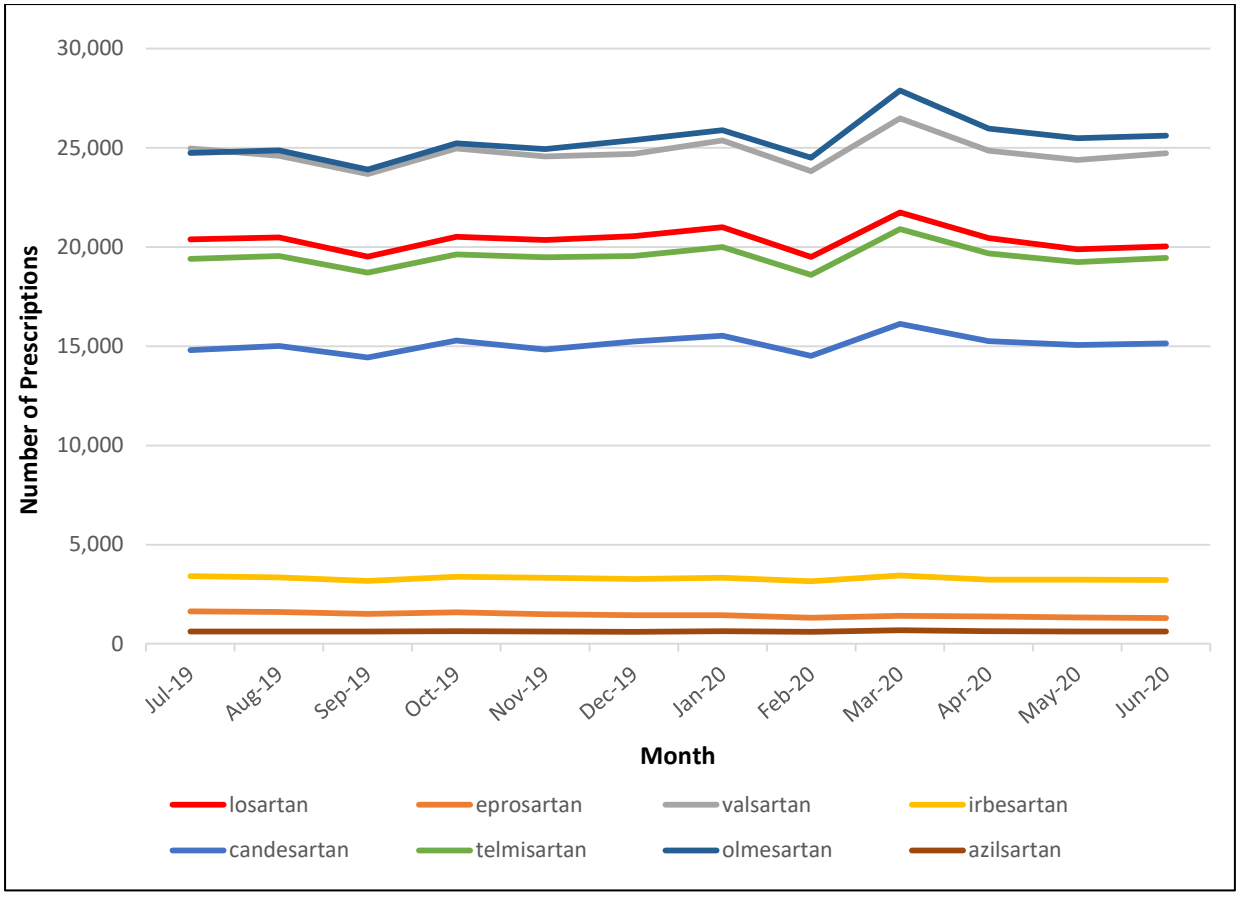

Figure 6: Number of prescriptions for ARBs on all community drug schemes July 2019 - June 2020

Figure 6 highlights that in the 12-month period from July 2019 to June 2020 inclusive, olmesartan was the most commonly prescribed ARB on all CDS; in July 2019 there were 24,748 prescriptions for olmesartan increasing to 25,615 prescriptions in June 2020. There was limited fluctuation in the number of prescriptions for all other ARBs.[6]

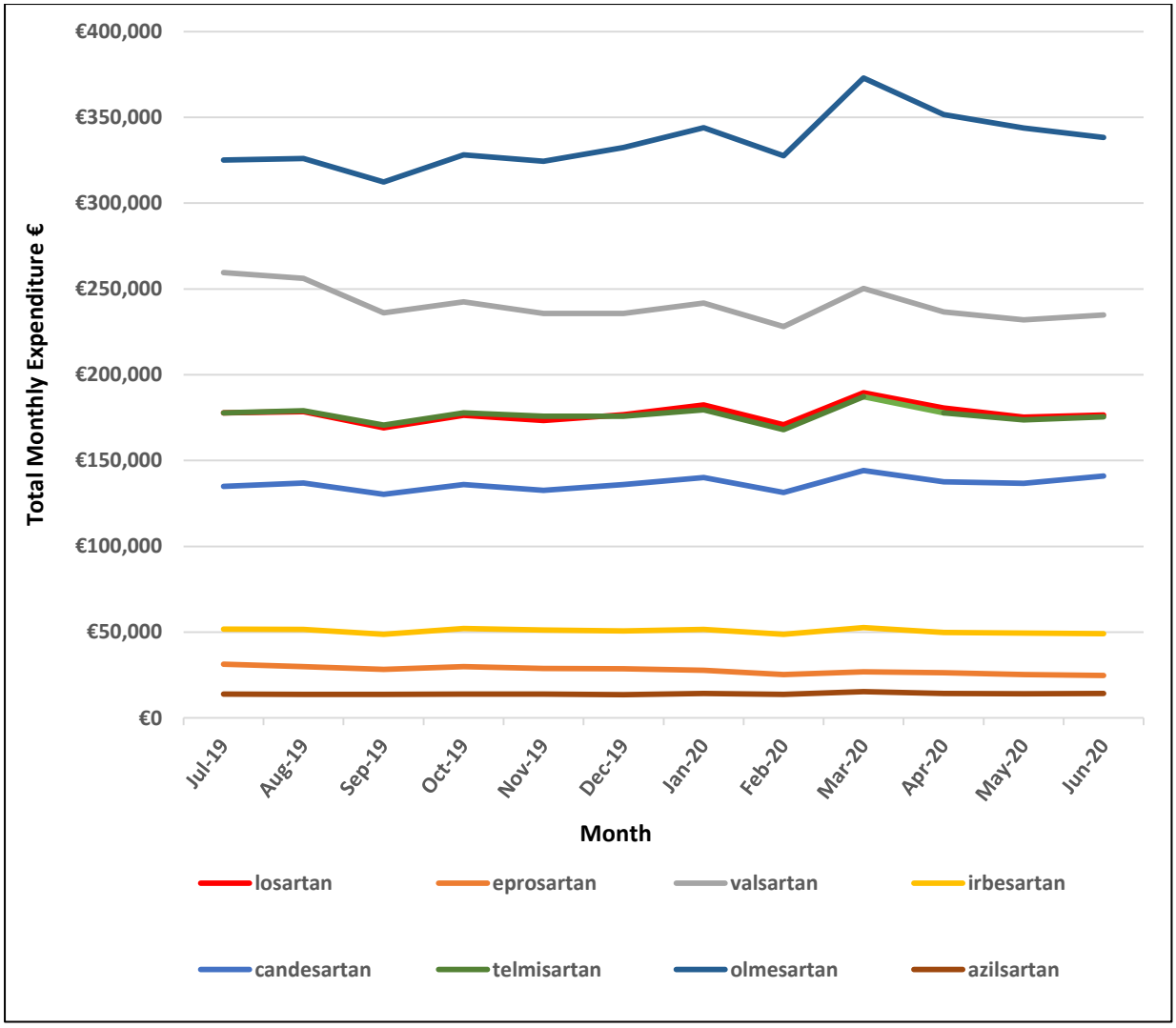

Figure 7: Total expenditure for each ARB on all community drug schemes July 2019 - June 2020

Figure 7 illustrates that total expenditure for ARBs on all CDS followed a similar trend. Overall, monthly expenditure was consistent over the 12-month period analysed, with a slight dip in February 2020 followed by an increase in March 2020 noted. The highest expenditure was observed for olmesartan followed by valsartan.[6]

Total ARB expenditure on CDS accounted for €13.9 million in the period from July 2019 - June 2020. Within that, the highest expenditure was on olmesartan (€4.03 million), followed by valsartan (€2.89 million), losartan (€2.13 million), telmisartan (€2.12 million), candesartan (€1.64 million), irbesartan (€0.6 million), eprosartan (€0.33 million) and azilsartan (€0.17 million).[6]

Table 8: Breakdown of total number of prescriptions for different strengths of ARBs on all community drug schemes from January 2019 - December 2019

ARB	Number of prescriptions*	Percentage of prescriptions
Azilsartan 20 mg	2,158	29.4%
Azilsartan 40 mg	3,219	43.8%
Azilsartan 80 mg	1,966	26.8%
Total	7,343	
Candesartan 2 mg**	1,259	0.8%
Candesartan 4 mg	45,492	28.1%
Candesartan 8 mg	63,365	39.2%
Candesartan 16 mg	50,703	31.4%
Candesartan 32 mg	788	0.5%
Total	161,607	
Eprosartan 400 mg	6,016	31.5%
Eprosartan 600 mg	13,088	68.5%
Total	19,104	
Irbesartan 75 mg	6,696	16.9%
Irbesartan 150 mg	18,162	45.8%
Irbesartan 300 mg	14,768	37.3%
Total	39,626	
Losartan 2.5 mg**	73	0%
Losartan 10 mg**	2	0%
Losartan 12.5 mg**	9,970	4.2%
Losartan 25 mg	3,693	1.6%
Losartan 50 mg	135,977	57.6%
Losartan 100 mg	86,513	36.6%
Total	236,228	
Olmesartan 10 mg	110,860	39%
Olmesartan 20 mg	124,603	43.8%
Olmesartan 40 mg	49,131	17.2%
Total	284,594	
Telmisartan 20 mg	52,370	23.9%
Telmisartan 40 mg	101,060	46.1%
Telmisartan 80 mg	66,021	30%
Total	219,451	
Valsartan 3 mg**	41	0%
Valsartan 40 mg	65,840	21.1%
Valsartan 80 mg	142,325	45.7%
Valsartan 160 mg	97,434	31.3%
Valsartan 320 mg	5,841	1.9%
Total	311,481	

*Cumulative number of prescriptions over the twelve-month period.

**Some strengths included are not licensed in the treatment of hypertension and/or heart failure but are included for reference.

Table 8 shows that the majority of prescriptions dispensed for all eights ARBs in the period from January 2019 to December 2019 were for the average strength preparation which correlates with the DDD of each ARB.[6]

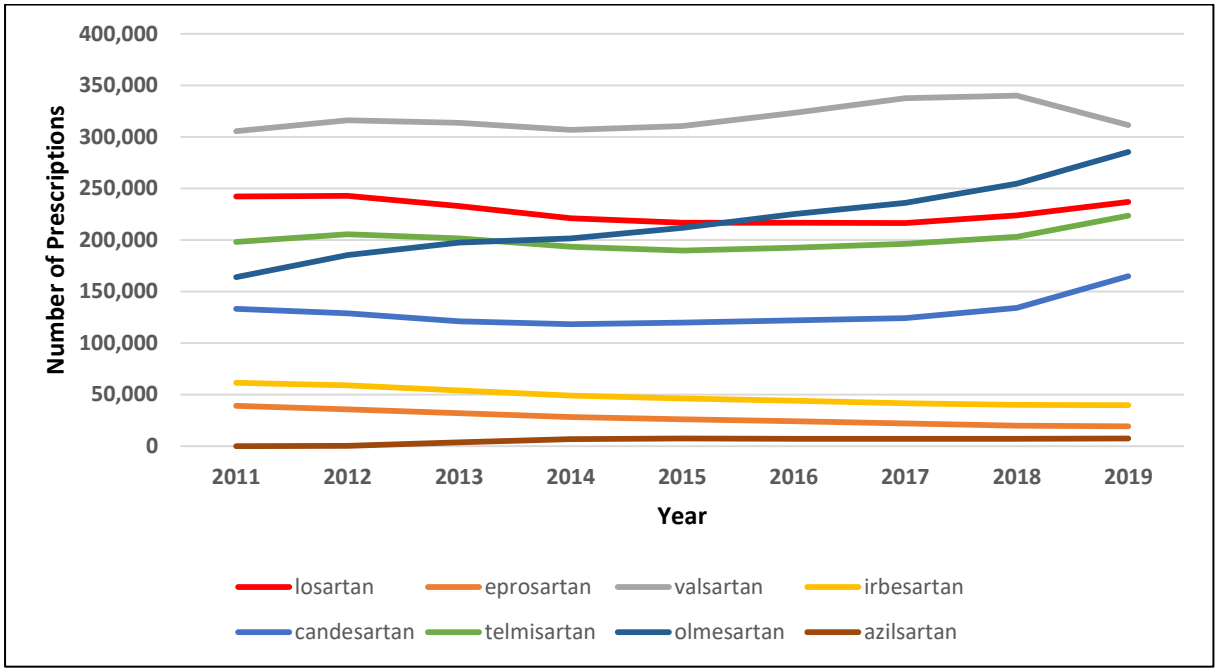

Figure 8: Total number of prescriptions annually for each ARB on all community drug schemes 2011 – 2019

Figure 8 illustrates that valsartan had the highest number of prescriptions from 2011 – 2019, with a decrease in number of prescriptions observed from 2018 to 2019. Olmesartan can be seen increasing substantially from 163,943 in 2011 to 285,509 in 2019. The MMP recommended candesartan as the preferred ARB in July 2014. In 2011, the total number of prescriptions for candesartan was 133,351. There was a decline in candesartan use from 2011 - 2014. From 2015, following the MMP's recommendation, prescribing of candesartan began to increase and as of 2019, the total number of prescriptions of candesartan on all CDS was 164,952 and is consistently rising. The percentage increase for candesartan following MMP's recommendation in 2014 to 2019 was 39%. The number of prescriptions dispensed under the CDS for olmesartan increased by 42% from 2014 to 2019. However, in terms of this review, olmesartan is only licensed in one indication, hypertension. There was a reduction in the number of prescriptions dispensed under the CDS for eprosartan (-32%) and irbesartan (-19%)

from 2014 to 2019. There were smaller increases for the rest of the ARBs- azilsartan (7%), losartan (7%), telmisartan (16%) and valsartan (2%).[6]

Olmesartan and valsartan command the greatest share of the ARBs on the community drug schemes. There has been a relatively large increase in the prescribing of candesartan and olmesartan in comparison to other ARBs since the MMP recommendation in 2014.

6. Nitrosamine impurity

In July 2018, the Health Products Regulatory Authority (HPRA) undertook a precautionary recall of a number of medicines containing the active ingredient valsartan due to the identification of a nitrosamine impurity, including N-nitrosodimethylamine (NDMA) which is classified as a probable human carcinogen. The HPRA statement indicated that there was no evidence to date that any harm had come to patients.[5,44]

As a result of this development, prescribers may have experienced a shortage of valsartan for a duration which had implications, as over 25,000 patients were in receipt of valsartan at that time. Therefore, many prescribers may have been required to discontinue valsartan products and prescribe alternative agents which may have resulted in a change to an alternative ARB. The MMP highlighted that candesartan was the preferred ARB and advised on approximate daily dose conversions from valsartan to candesartan.[5,44]

In September 2018, it was announced that the EU-wide review of the valsartan impurity issue would be expanded to include medicines containing four other 'sartans', namely candesartan, irbesartan, losartan and olmesartan.[5] The EMA's committee for medicinal products for human use (CHMP) has aligned recommendations for limiting nitrosamine impurities in sartan medicines with recent recommendations it issued for other classes of medicines. The main change concerns the limits for nitrosamines, which previously applied to the active

ingredients but will now apply instead to the finished products (e.g. tablets). These limits, based on internationally agreed standards, should ensure that the excess risk of cancer from nitrosamines in any sartan medicines is below 1 in 100,000 for a person taking the medicine for lifelong treatment.[45]

The EMA outlines that in line with previous recommendations, companies should have appropriate control strategies to prevent or limit the presence of nitrosamine impurities as much as possible and, where necessary, improve their manufacturing processes. Companies should also evaluate the risk of nitrosamines being present in their medicines and carry out appropriate tests. In the vast majority of sartan medicines, these impurities were either not found or were present at very low levels.[45]

As of the time of publication, there is a product shortage notification for losartan, due to manufacturing delays with the return date currently unknown. Telmisartan is experiencing a shortage due to an unexpected increase in demand but it is expected to be resolved by February 2022.[5]

As of the 6th August 2021, the HPRA has advised that as a precautionary measure, specific batches of sartan-containing products are being recalled to pharmacy level in Ireland. The reason for this recall is due to the presence of an impurity called 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole (termed an 'azide' impurity), which has mutagenic potential. At present, there is no evidence that this impurity has caused any harm to patients and therefore this pharmacy-level recall is being undertaken as a precautionary measure. Specific batches are being recalled in cases where the impurity is above regulatory acceptable levels.[5]

7. Conclusion

Following a review of the available clinical evidence and taking into account the following criteria: licensed therapeutic indications, clinical outcome data, national and international clinical guidelines, adverse drug reaction profiles, cautions and contraindications, drug interaction profiles, patient factors, cost and national prescribing trends, candesartan is recommended by the MMP as the preferred ARB for the treatment of hypertension and heart failure.

Based on the current evidence candesartan is the MMP's preferred ARB for the treatment of hypertension and heart failure.

- ✓ **Candesartan is licensed for the treatment of hypertension and heart failure.**
- ✓ **Candesartan has once-daily dosing for all indications under review.**
- ✓ **Candesartan has a favourable adverse drug reaction profile.**
- ✓ **Candesartan has a favourable drug interaction profile.**
- ✓ **Candesartan has a favourable cost profile across all available strengths.**

8. References

1. Health Service Executive. Medicines Management Programme. 7th July 2014. Preferred Drugs: Angiotensin-II Receptor Blockers (ARBs). Accessed at https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/angiotensin-ii-receptor-blockers-arbs-.pdf on 02/02/2022.
2. Tsoi B, Akioyamen L, Bonner A *et al.* Comparative Efficacy of Angiotensin II Antagonists in Essential Hypertension: Systematic Review and Network Meta-Analysis of Randomised Controlled Trials. *Heart Lung and Circulation.* 2018;27:666-682.
3. British National Formulary (BNF). 2022 . Pharmaceutical Press. [Online]. Accessed at https://www.new.medicinescomplete.com/#/. on 12/01/2022.
4. Health Service Executive Primary Care Reimbursement Service. Search reimbursable items. Accessed at https://www.sspcrs.ie/druglist/pub on 02/02/2022.
5. Health Products Regulatory Authority (HPRA). Human medicines listing. Accessed at https://www.hpra.ie on 02/02/2022.
6. HSE-PCRS database-total expenditure on ARBs (January 2011-June 2020). On file.
7. Edarbi® 20 mg/ 40 mg/ 80 mg tablets (Azilsartan). Takeda Pharma A/S. Summary of Product Characteristics. Last revised 10/02/2021. Accessed at www.ema.europa.eu on 02/02/2022.
8. Atacand® 4 mg tablets (Candesartan). Summary of Product Characteristics. Last revised February 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2239-010-001_05022021150553.pdf on 02/02/2022.
9. Atacand® 8 mg tablets (Candesartan). Summary of Product Characteristics. Last revised February 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2239-010-002_05022021150553.pdf on 02/02/2022.
10. Atacand® 16 mg tablets (Candesartan). Summary of Product Characteristics. Last revised February 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2239-010-003_05022021150553.pdf on 02/02/2022.
11. Teveten® 400 mg film coated tablets (Eprosartan). Summary of Product Characteristics. Last revised November 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2010-017-001_23112020201120.pdf on 02/02/2022.
12. Teveten® 600 mg film coated tablets (Eprosartan). Summary of Product Characteristics. Last revised November 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2010-017-002_23112020201120.pdf on 02/02/2022.
13. Aprovel® 75 mg/ 150 mg/ 300 mg tablets (Irbesartan). Sanofi-Aventis Groups. Summary of Product Characteristics. Last revised 22/04/2021. Accessed at www.ema.europa.eu on 02/02/2022.
14. Cozaar® 12.5 mg film coated tablets (Losartan). Summary of Product Characteristics. Last revised July 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA23198-002-001_30072021165106.pdf on 02/02/2022.

15. Cozaar® 50 mg film coated tablets (Losartan). Summary of Product Characteristics. Last revised July 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA23198-002-002_30072021165107.pdf on 02/02/2022.
16. Cozaar® 100 mg film coated tablets (Losartan). Summary of Product Characteristics. Last revised July 2021. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA23198-002-003_30072021165106.pdf on 02/02/2022.
17. Olmesartan Medoxomil 10 mg film coated tablets (Olmesartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-113-001_19062020155847.pdf on 02/02/2022.
18. Olmesartan Medoxomil 20 mg film coated tablets (Olmesartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-113-002_19062020155847.pdf on 02/02/2022.
19. Olmesartan Medoxomil 40 mg film coated tablets (Olmesartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-113-003_19062020155847.pdf on 02/02/2022.
20. Micardis® 20 mg/ 40 mg/ 80 mg tablets (Telmisartan) Boehringer Ingelheim International GmbH. Summary of Product Characteristics. Last revised 28/09/2021. Accessed at www.ema.europa.eu on 02/02/2022.
21. Diovan® 40 mg film coated tablets (Valsartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-009-003_30062020113703.pdf on 02/02/2022.
22. Diovan® 80 mg film coated tablets (Valsartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-009-001_30062020113701.pdf on 02/02/2022.
23. Diovan® 160 mg film coated tablets (Valsartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-009-002_30062020113703.pdf on 02/02/2022.
24. Diovan® 320 mg film coated tablets (Valsartan). Summary of Product Characteristics. Last revised June 2020. Accessed at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0896-009-004_30062020113704.pdf on 02/02/2022.
25. Williams B, Mancia G, Spiering W *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the ESH (ESH). *Eur Heart J* 2018;39(33):3021-3104.
26. European Society of Cardiology. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Accessed at www.escardio.org on 02/02/2022.

27. Mazza A, Sacco A P, Townsend D *et al.* Cost-benefit effectiveness of angiotensin-II receptor blockers in patients with uncomplicated hypertension: A comparative analysis. *Biomed Pharmacother.* 2017;90:665-669.
28. Luan L, Hu H, Li SC. Angiotensin II Type 1 Receptor Blockers. *Value Health*.2018;21(2):S35.
29. Irish College of General Practitioners. Cardiovascular disease: prevention in general practice (2021). Accessed at www.icgp.ie on 02/02/2022.
30. National Institute for Health and Care Excellence. National Guideline 136: Hypertension in adults: diagnosis and management (2019). Accessed at www.nice.org.uk on 02/02/2022.
31. Unger T, Borghi C, Charchar F *et al.* 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* 2020;75(6):1334-1357.
32. Whelton P, Carey R, Aronow W *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71(6):1269-1324.
33. Clarity's Diagnosis and Treatment Guidance. Hypertension. [Last updated April 2021]. Accessed at http://medicinescomplete.com on 02/02/2022.
34. British and Irish Hypertension Society. Hypertension Management. Accessed at https://bihsoc.org/guidelines/hypertension-management/ on 02/02/2022.
35. Irish College of General Practitioners. Heart Failure in General Practice (2019). Accessed at https://www.icgp.ie/index.cfm?spKey=in_the_practice.quick_reference_guides.quick_reference_guides_qrg_.cardiovascular_health on 02/02/2022.
36. National Institute for Health and Care Excellence. National Guideline 106: Chronic Heart Failure in adults: diagnosis and management (2018). Accessed at www.nice.org.uk on 02/02/2022.
37. Yancy C, Jessup M, Bozkurt B *et al.* 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;70(6):776-803.
38. Clarity's Diagnosis and Treatment Guidance. Heart failure- chronic. [Last updated August 2021]. Accessed at http://medicinescomplete.com on 02/02/2022.
39. Health Service Executive. Medicines Management Programme. Sacubitril/Valsartan (Entresto®) Clinical and Reimbursement Information. November 2017. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/managed-access-protocols/sacubitril-and-valsartan-entresto/sacubitril-and-valsartan-entresto-clinical-and-reimbursement-information.pdf on 02/02/2022.
40. European Medicines Agency. Restriction of combined use of medicines affecting the renin-angiotensin system (RAS). Accessed at https://www.ema.europa.eu/en/news/combined-use-medicines-affecting-renin-angiotensin-system-ras-be-restricted-chmp-endorses-prac on 02/02/2022.

41. Yang R, Luo Z, Liu Y *et al.* Drug Interactions with Angiotensin Receptor Blockers: Role of Human Cytochromes P450.*Curr Drug Metab.* 2016;17(7):681-91.
42. Unger T, Kaschina E. Drug interactions with angiotensin receptor blockers: a comparison with other antihypertensives. *Drug Saf.*2003;26(10):707-20.
43. World Health Organisation (WHO) Collaborating Centre for Drug Statistics and Methodology. 2017. Define daily dose. Accessed at https://www.whocc.no/atc_ddd_index/?code=C09CA&showdescription=yes on 02/02/2022.
44. Health Service Executive. Medicines Management Programme. Guidance on shortages. MMP Guidance for Prescribers on valsartan shortage- July 2018. Accessed at https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/guidance-on-shortages/mmp-guidance-for-prescribers-on-valsartan-shortage-july-2018.pdf on 14/01/2022.
45. European Medicines Agency. Nitrosamines: EMA aligns recommendations for sartans with those for other medicines. Accessed at https://www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines on 02/02/2022.

9. Bibliography

- Zheng Z, Shi H, Jia J *et al.* A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension. *J Renin Angiotensin Aldosterone Syst.*2011;12(3):365-74.
- Heran BS, Yong MMY, Heran IK *et al.* Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev* 2008;8;2008(4):CD003822.
- Hudson M, Humphries K, Tu J *et al.* Angiotensin II receptor blockers for the treatment of heart failure: a class effect? *Pharmacotherapy.* 2007;27(4):526-34.
- Desai R, Ashton C, Deswal A *et al.* Comparative effectiveness of individual angiotensin receptor blockers on risk of mortality in patients with chronic heart failure. *Pharmacoepidemiol Drug Saf.* 2012;21(3):233-40.
- Tongbram V, Shah D, Khan N. Comparative effectiveness of angiotensin receptor blockers in chronic heart failure: A network meta-analysis. *Value Health*.2013;16(3):A275.
- Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-1675.
- Abraham H, White M, White W. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf.* 2015;38(1):33-54.