Medicines Management Programme

Preferred Drugs

Calcium Channel Blockers

(dihydropyridine derivatives)

for the treatment of hypertension and stable angina

Approved by	Prof. Michael Barry, Clinical Lead, MMP.
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Contents

1. Purpose 1

2. Definitions 2

3. Classification of calcium channel blockers 2

4. Preferred drug 4

5. Consultation for calcium channel blockers 4

6. Selection criteria for calcium channel blocker review 4

6.1 Licensed therapeutic indications 4

6.1.1 Hypertension 5

6.1.1.1 Clinical efficacy in hypertension 5

6.1.1.2 Systematic reviews of hypertension 14

6.1.1.3 Clinical guidelines for hypertension 17

6.1.2 Angina 18

6.1.2.1 Clinical efficacy of stable angina 18

6.1.2.2 Systematic reviews of stable angina 21

6.1.2.3 Clinical guidelines for stable angina 22

6.2 Patient factors 24

6.2.1 Dosing and administration 24

6.3 Cautions and contraindications 25

6.4 Adverse drug reactions (ADRs) 25

6.5 Drug interactions 27

6.6 Cost 29

6.7 Prescribing trends in Ireland 30

7. Summary 31

8. References 32

Bibliography 37

Appendix A 39

Tables

Table 1: Classification of dihydropyridine calcium channel blockers 2
Table 2: Licensed indications of dihydropyridine calcium channel blockers 5
Table 3: Calcium channel blocker trials in hypertension included in this review 6
Table 4: Meta-analyses of calcium channel blockers under review 14
Table 5: Reviews of calcium channel blockers 14
Table 6: Review of clinical guidelines for hypertension 17
Table 7: Calcium channel blocker trials for stable angina included in this review 19
Table 8: Meta-analyses and reviews of CCBs in stable angina 21
Table 9: Review of clinical guidelines for stable angina 23
Table 10: Dosing regimen for calcium channel blockers 24
Table 11: Cautions and contraindications for calcium channel blockers 25
Table 12: Description of the frequency of adverse drug reactions 25
Table 13: Common/very common adverse drug reactions of calcium channel blockers 26
Table 14: Drugs which are known to induce or inhibit CYP3A4 27
Table 15: The defined daily dose for each calcium channel blocker 29

Figures

Figure 1: Reimbursement cost per month (28 days), exclusive of pharmacist fees and mark-up, of available CCBs based on the defined daily dose (DDD) 29
Figure 2: Market share of calcium channel blockers, per number of prescriptions (GMS) Oct 2014 - Oct 2015. 30

List of abbreviations

ACC	American College of Cardiology
ADR	Adverse drug reaction
AHF	American Heart Foundation
ACE	Angiotensin converting enzyme
AHA	American Heart Association
ARB	Angiotensin II receptor blocker
BP	Blood pressure
CCB	Calcium channel blocker
CHD	Coronary heart disease
CPU	Corporate Pharmaceutical Unit
CVD	Cardiovascular disease
DDD	Defined daily dose
DHP	Dihydropyridine
ER	Extended release
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GMS	General Medical Scheme
GITS	Gastrointestinal therapeutic system
HR	Heart rate
HTN	Hypertension
HPRA	Health Products Regulatory Authority
MI	Myocardial infarction
MMP	Medicines Management Programme
NICE	National Institute for Health and Care Excellence
PCRS	Primary Care Reimbursement Service
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
WHO	World Health Organisation

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1. Purpose

Calcium channel blockers (CCBs) were initially developed in the 1960s[1] and are used in the treatment of various cardiovascular diseases including angina, hypertension and Raynaud's disease.[2] CCBs inhibit the inward-flow of calcium ions causing systemic vasodilation.[3] There are three classes of CCBs: dihydropyridine (DHP), phenylalkylamine and benzothiazepine derivatives.[4] These classes differ in chemical structure and binding sites resulting in differing cardiac effects.[5]

The DHP CCBs (e.g. amlodipine) cause reflex activation of the sympathetic nervous system, increasing heart rate and cardiac output. In contrast the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) CCBs cause a modest decrease in heart rate, A-V conduction and cardiac output.[6] Verapamil and diltiazem, referred to as rate-limiting CCBs, are often used to treat arrhythmias.[7] The differing properties between classes of CCBs means that they cannot be used interchangeably. This document aims to select a preferred DHP CCB, as verapamil and diltizem are rate-limiting CCBs they will not be included in this review.

There are six licensed DHP CCBs in Ireland: amlodipine, felodipine, lercanidipine, nifedipine, nilvadipine and nimodipine.[8] Nimodipine has a specialist indication in the treatment of aneurysmal subarachnoid haemorrhage, therefore it will not be considered in this review.[9]

In 2014 expenditure on DHP CCBs on the General Medical Services (GMS) scheme exceeded €16.5 million.[10] Expenditure has decreased in recent years due to generic substitution and reference pricing. However the DHP CCBs are still the 17th most expensive class of drug on the GMS scheme, with amlodipine the 9th most commonly prescribed drug.[10]

The selection by the Medicines Management Programme (MMP) of a preferred CCB, is designed to support prescribers in choosing a medicine of proven safety and efficacy, in the management of patients with hypertension and stable angina. The MMP aims to enhance the quality of prescribing and provide value for money. Prescribers are encouraged to consider the preferred drug when initiating a CCB or when switching from another CCB, when a change in drug treatment is indicated. This guidance is not applicable to all patient populations, it does not include children or patients

with hepatic or renal disease, where specialist advice should be sought. The use of CCBs is not recommended during pregnancy unless the clinical benefits outweigh the risk to the foetus.[2]

2. Definitions

- For the purposes of this review the term calcium channel blocker refers to DHP CCBs. Only DHP CCBs, reimbursed and licensed for hypertension and/or stable angina, were reviewed in this document. Where two or more preparations of the same drug are listed (e.g. where there are different manufacturers/suppliers), the least expensive preparation has been selected for the evaluation. Costs are correct as of March 2016.[11]

- The defined daily dose (DDD) is obtained for each drug using the ATC code. This code is a World Health Organisation method for classifying drugs, based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties.[12]

3. Classification of calcium channel blockers

DHP CCBs can be divided into first, second and third generation agents according to their pharmacokinetic and pharmacodynamic properties (table 1).[13]

Table 1: Classification of dihydropyridine calcium channel blockers.[13-20]

Drug	Classification
Nifedipine (immediate-release)	First generation
Nifedipine long-acting (slow-release or GITS *)	Second generation, subclass A
Felodipine	Second generation, subclass B
Nilvadipine	Second generation, subclass B
Amlodipine	Third generation
Lercanidipine	Third generation

* GITS: Gastrointestinal therapeutic system

The first generation CCBs (e.g. nifedipine immediate-release) have a rapid onset and short duration of action, therefore multiple daily dosing is required.[13,14] These drugs reduce both myocardial contractility and the conduction of electrical impulses to the heart, and also cause reflex tachycardia. These side effects are particularly unwanted when treating patients recovering from an acute MI, or patients with left ventricular dysfunction.[13]

Nifedipine immediate-release should only be used for the treatment of hypertension or chronic stable angina if no other treatment is appropriate due to the dose-dependent increased risk of cardiovascular complications and mortality.[14] NICE guidance on hypertension states that only long-acting formulations of nifedipine should be considered for the treatment of hypertension.[21] Nifedipine immediate-release will therefore not be considered further in this review.

Second generation DHP CCBs were developed in order to improve the pharmacokinetic profile and reduce the unwanted side effects of first generation CCBs, with a longer duration of action and enhanced vascular selectivity.[13] There are two subclasses of CCBs in this group, the first (subclass A) comprises the modified release formulations which have an extended duration of action e.g. nifedipine slow-release (SR) or gastrointestinal therapeutic system (GITS).[15,16] The second (subclass B) is comprised of chemical entities which have less negative effect on myocardial contractility and heart rate and reduced effect on atrioventricular conduction (e.g. nilvadipine).[18] In clinical trials nilvadipine demonstrated a longer duration of action and a vasodilatory effect 5-16 times greater than nifedipine immediate-release.[22] However despite these advantages second generation CCBs continue to demonstrate practical problems, such as fluctuations in antihypertensive effect over 24 hours and difficulty with bioavailability in extended release formulations.[13]

Third generation CCBs interact with specific high affinity binding sites in the calcium channel complex.[13] These CCBs do not exhibit the drug-induced autonomic activation which occurs in previous generations of CCBs, causing potentially detrimental effects in patients with left ventricular dysfunction.[13] Amlodipine and lercanidipine are examples of third generation CCBs.[4]

Amlodipine has a gradual onset and prolonged duration of action due to its long plasma half-life (40-50 hours).[13] At physiological pH amlodipine is in the ionised state, therefore it combines more slowly with the receptor and binds more firmly to various tissue compartments.[4] Lercanidipine is a lipophilic DHP CCB. Lercanidipine accumulates in the lipid bilayer of cell membranes where it is released slowly and gradually, close to the target calcium channels, enabling it to have a long half-life.[6] This slow onset of action prevents reflex tachycardia and sympathetic activation. Lercanidipine demonstrates increased vascular selectivity and less of a negative effect on myocardial contractility than other CCBs.[6,23]

4. Preferred drug

Preferred calcium channel blocker

AMLODIPINE is the preferred dihydropyridine calcium channel blocker.

5. Consultation for calcium channel blockers

A period of consultation was undertaken in which submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on 18th March 2016.

6. Selection criteria for calcium channel blocker review

A number of key criteria were considered in the selection process:

- Licensed indications
- Clinical outcome data
- Comparative efficacy
- Clinical guidelines
- Patient factors
  - Dosing and administration
- Cautions and contraindications
- Adverse effects
- Drug interactions
- Cost
- National prescribing trends

6.1 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 DHP CCBs for hypertension and stable angina the preferred CCB should be licensed for at least these two indications. All DHP CCBs considered in this review are licensed to treat hypertension. Amlodipine, nifedipine long-acting and felodipine are also licensed to treat stable angina (table 2).[15-20]

Table 2: Licensed indications of dihydropyridine calcium channel blockers

Drug	Hypertension	Angina
Nifedipine long-acting (SR or GITS*)[15,16]	All grades of hypertension	Chronic stable angina pectoris as monotherapy or combination with a beta blocker
Felodipine[17]	Hypertension	Stable angina pectoris
Nilvadipine[18]	Essential hypertension	Not licensed**
Amlodipine[19]	Hypertension	Chronic stable angina pectoris, vasospastic angina
Lercanidipine[20]	Mild to moderate essential hypertension	Not licensed**

*SR: Slow-release; GITS: Gastrointestinal therapeutic system. **Currently not licensed (31 March 2016)

Amlodipine, nifedipine long-acting and felodipine are licensed for both hypertension and stable angina.

6.1.1 Hypertension

6.1.1.1 Clinical efficacy in hypertension

The safety and efficacy of the preferred CCB should be demonstrated in high quality randomised controlled trials (RCTs) and other published studies.

A literature search was carried out to identify the main clinical trials of CCBs used to treat hypertension. The following databases were used: EMBASE (1947-2016), MEDLINE (1946-2016) and CINAHL (1937-2016). The clinical trials examined are outlined in table 3. This list is not exhaustive but represents the most significant trials of CCBs in hypertension. Further clinical trials considered as part of the review process can be found in the bibliography. The key findings are summarised as follows:

Table 3: Calcium channel blocker trials in hypertension included in this review

Trial	Design	Drugs used in trial	Findings
ACCOMPLISH[24] 2007	Multi centre, double-blind, RCT, n=11,506	Benazepril- **amlodipine** vs. benazepril-hydrochlorothiazide	Reduction in BP was similar from baseline for both groups. There was a mean reduction in BP of 0.9/1.1mmHg between the groups (p<0.001). Risk of cardiovascular events and death was lower with the benazepril-amlodipine group (absolute risk reduction 2.2%).
VALUE [25] 2004	Multi centre, double-blind, RCT, n=15,245	**Amlodipine** vs. valsartan	Both groups lowered BP, amlodipine significantly more than valsartan (p<0.001). The composite endpoint of time to first cardiac event did not differ between the treatment groups (p=0.49). The mean patient follow up time was 4.2 years.
ASCOT-BPLA[26] 2005	Multi centre, RCT, n=19,257	**Amlodipine** +/- perindopril vs. atenolol +/- bendroflumethiazide	BP was lower throughout the trial in the amlodipine group. Average difference in BP was 2.7/1.9mmHg (p<0.0001). Primary endpoint of non-fatal MI and fatal CHD was 10% lower in the amlodipine group, but this was not significant.
CAMELOT[27] 2004	Multi centre, double-blind, RCT, n=1,991	Comparison of **amlodipine**, enalapril or placebo	Antihypertensive treatment with either drug significantly lowered BP vs. placebo p<0.001. There was no significant difference in primary endpoint of cardiovascular events between the two treatments (p=0.1).
ALLHAT[28] 2002	Multi centre, double-blind, RCT, n=33,357	**Amlodipine** vs. chlorthalidone vs. lisinopril	Thiazide diuretics were superior in preventing one or more forms of CVD. Five year systolic BP results were significantly higher in amlodipine and lisinopril groups (p<0.001) than chlorthalidone, however diastolic BP was significantly lower in the amlodipine group (p<0.001).
Long-term treatment with lercanidipine in patients with mild to moderate hypertension[29] 1997	Open, multi centre n=355	**Lercanidipine** Diuretic, ACE or beta-blocker added if needed	After 4 weeks lercanidipine caused a significant decrease in BP (p<0.001). Thirty-one (8.7%) patients complained of side effects, 4% of patients withdrew due to side effects.
ELYPSE[30] 2002	Multi centre, open prospective observational study, n=9,059	**Lercanidipine**	Significant reductions in systolic and diastolic BP were observed after one month (p<0.001). 6.5% of patients had an adverse reaction. Most commonly headache (2.9%), oedema (1.2%), flushing (1.1%) and palpitations (0.6%).
LEAD[31] 2003	Multi centre, double-blind, parallel group n=250	**Lercanidipine** vs. **felodipine** vs. **nifedipine GITS**	All of the DHPs studied significantly and equally decreased BP after 4 weeks. The number of ADRs was significantly lower in lercanidipine and nifedipine GITS patients compared to felodipine (p<0.05). There was no significant difference in ADRs between lercanidipine and nifedipine GITS.

ELLE[32] **2003**	Multi centre, randomised, parallel group comparison trial, n=324	**Lercanidipine** vs. **lacidipine*** vs. **nifedipine GITS**	Systolic and diastolic BP was significantly decreased in all three study groups compared to baseline (p<0.01). Incidence of ADRs was lowest in the lercanidipine group (19.4%).
Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives[33] **2002**	Multi centre, double-blind, parallel study n=828	**Lercanidipine** vs. **amlodipine** vs. **lacidipine***	BP was significantly and equally decreased in all treatment groups (p<0.01). Incidence of oedema was significantly higher in the amlodipine group 19% (p<0.001) compared to lercandipine (9.3%) and lacidipine* (4.3%) groups.
Effects of lercanidipine vs. amlodipine in hypertensive patients with cerebral ischemic stroke[34] **2015**	Open label, controlled, randomised, parallel-group study, n=104	**Lercanidipine** vs. **amlodipine**	BP was significantly decreased in both treatment groups. There was no statistical difference in BP between the two groups. There were less adverse events in the lercanidipine group compared to the amlodipine group (5.7% compared to 19.2%).
HOT[35] **1994**	PROBE n=18,790	**Felodipine** Aspirin Addition of ACE inhibitor, beta-blocker or diuretic if needed to obtain target BP	Patients were randomly assigned to one of three target BP groups: ≤90mmHg, ≤85mmHg and ≤80mmHg. Felodipine reduced BP by a similar amount in all 3 target groups. The lowest incidence of cardiovascular events occurred with a mean diastolic BP of 82.6 mmHg. Addition of aspirin reduced the risk of acute MI without increasing the risk of bleeding.
STOP-Hypertension-2[36] **1999**	PROBE n=6,614	**1.** Conventional drug group: Atenolol/ metoprolol/pindolol or hydrochlorothiazide plus amiloride **2.** ACE inhibitor group: enalapril or lisinopril. **3.** CCB group: **felodipine** or **isradipine***	BP was lowered by a similar amount in all three therapeutic regimens from baseline values. There was no significant difference between old and new antihypertensive regimens for primary combined endpoint of fatal stroke, fatal MI and other fatal CVD (p=0.89).

Lercanidipine hydrochloride versus felodipine sustained-release for mild-to-moderate hypertension: a multi-centre, randomised clinical trial[37] 2015	Multi centre, RCT, open-label, parallel group, n=281	**Lercanidipine** vs. **felodipine**	There was a significant decrease in BP compared to baseline for lercanidipine and felodipine (p<0.0001). There was no significant difference between groups for BP lowering. ADRs were 26.6% in the lercanidipine group and 25.3% in the felodipine group.
INSIGHT[38] 2000	Prospective, RCT, double-blind trial n=6,321	**Nifedipine GITS** vs. co-amilozide	After titration BP remained close to 138/82mmHg in both groups. Primary endpoints were cardiovascular death, MI, heart failure or stroke. There was no significant difference in primary endpoints between Nifedipine GITS and co-amilozide. There were 8% more withdrawals in the nifedipine group from peripheral oedema (p<0.0001), however serious adverse events were more frequent in the co-amilozide group.
Treatment of mild-to-moderate hypertension with CCBs: comparison of nifedipine GITS with amlodipine[39]	Multi centre, parallel group, double-blind RCT n=155	**Nifedipine GITS vs. amlodipine**	The primary criterion for assessing efficacy between drugs was mean diastolic BP. Both groups reduced BP (p<0.001). There was no significant difference in BP lowering between the 2 groups. The incidence of adverse effects was 7.9% in the nifedipine group and 10.1% in the amlodipine group.
Comparison of the efficacy of nilvadipine and nitrendipine on circadian blood pressure[40] 1992	Double-blind, placebo controlled trial, n=183	**Nilvadipine** vs. **nitrendipine***	Nilvadipine was significantly better at lowering systolic and diastolic BP than placebo and slightly better than nitrendipine. Nilvadipine had a more sustained duration of action than nitrendipine and less side effects. Peripheral oedema incidence was 29% with nitrendipine and 5% with nilvadipine.
Effects of nilvadipine and amlodipine in patients with mild/moderate essential hypertension[41] 2005	Double-blind, parallel group, RCT, n=168	**Nilvadipine** vs. **amlodipine**	There was no significant difference between BP lowering in the two treatment groups (p=0.22). There was also no significant difference in ADRs between groups. Lower limb oedema was the most frequent event leading to study withdrawal.

CCB: Calcium channel blocker; ACE: Angiotensin converting enzyme; ARB: Angiotensin-II receptor blocker; RCT: Randomised controlled trial; PROBE: Prospective, randomised, open with blinded endpoint evaluation.
* Not licensed in Ireland

Key findings from clinical efficacy in hypertension

Amlodipine

The efficacy of amlodipine in the treatment of hypertension has been demonstrated in numerous large scale multi-centre RCTs. Amlodipine has also been compared to other DHP CCBs (see under individual drugs below).

- The 2007 ACCOMPLISH trial (n=11,506) involved participants from five countries with hypertension and a high risk of cardiovascular events. The trial compared amlodipine plus an ACE inhibitor versus a thiazide plus an ACE inhibitor. Reduction in BP (blood pressure) from baseline was similar in both groups over the course of the trial. The mean difference in BP between groups was 0.9mmHg systolic and 1.1mmHg diastolic ($p<0.001$, for systolic and diastolic pressures). The primary endpoint was time to first event i.e. a cardiovascular event or death from cardiovascular causes. The combination of ACE inhibitor plus amlodipine was found to be superior to ACE inhibitor plus a diuretic in reducing the risk of cardiovascular events and death in these patients (absolute risk reduction 2.2%, $p<0.001$).[24]

- The 2004 VALUE trial (n=15,245) investigated if valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk. Both groups lowered BP, however amlodipine was found to reduce BP significantly more than valsartan ($p<0.0001$) especially in the first month of treatment. The primary composite endpoint was time to first cardiac event, this did not differ significantly between groups ($p=0.49$).[25]

- The 2005 ASCOT-BPLA trial (n=19,257) investigated the prevention of cardiovascular events with amlodipine compared to atenolol based regimens. BP was lower in the amlodipine treatment regimen throughout the trial. The average difference in BP between the groups was 2.7/1.9mmHg ($p<0.0001$). The primary endpoint of non-fatal MI or fatal CHD was 10% lower in the amlodipine compared to the atenolol regimen, although this was not significant ($p=0.1$). Secondary endpoints included all-cause mortality, total stroke, total cardiovascular events including procedures and cardiovascular mortality. There was a significant reduction in all secondary endpoints (except fatal and non-fatal heart failure) with the amlodipine regimen.[26]

- In the 2004 CAMELOT trial (n=1,991 patients) amlodipine was compared with enalapril to determine the effect of these drugs on cardiovascular events in patients with coronary artery disease. Both antihypertensives were found to significantly lower BP compared to placebo ($p<0.001$). Primary endpoint was the incidence of cardiovascular events. Comparison between amlodipine and enalapril found there was no significant difference between treatments for the primary endpoint ($p=0.1$).[27]

- The 2002 ALLHAT trial (n= 33,357) involved 623 North American centres. Each participant was aged >55 years, with hypertension and at least one other risk factor for CVD. The participants were randomly assigned to either a diuretic, ACE inhibitor or calcium channel blocker (amlodipine). At the five-year follow-up, the participants systolic BP was reduced in all groups from baseline levels. However in comparison between groups systolic BP was found to be significantly higher in the amlodipine (0.8mmHg) and lisinopril groups (2mmHg, $p<0.001$), compared to the chlorthalidone group. There was no significant difference between treatments for the primary outcome of combined fatal coronary heart disease (CHD) or non-fatal MI, and all-cause mortality did not differ between groups.[28]

Lercanidipine

Lercanidipine is a third generation CCB. Clinical trials have demonstrated the efficacy of lercanidipine as an antihypertensive and shown it to have better tolerability than the older generation CCBs. A limitation of some of the lercanidipine trials was small sample size.[31,34,37]

- The long-term tolerability and antihypertensive effect of lercanidipine was initially studied by Cafiero and Glasi (1997). The drug was given at a dose of 10mg daily, then increased every 4 weeks if required up to 30mg daily. If this still did not control BP another class of antihypertensive was added. After 4 weeks treatment with lercanidipine, patients were found to have a significant reduction in BP ($p<0.001$). Only 3.4% of patients required combination therapy. Adverse-events occurred in 8.7% of patients and included flushing, headache, tachycardia and ankle oedema.[29]

- The findings of Cafiero and Glasi (1997) were also demonstrated in the ELYPSE study (2002), to determine the efficacy and tolerability of lercanidipine in clinical practice.[30] Significant reductions in BP were demonstrated after one month ($p<0.001$), further reductions in BP were demonstrated up

to three months. At the end of this observational study 64% of patients had achieved a diastolic BP <90mmHg. Adverse events occurred in 6.5% of patients. These included headache (2.9%), ankle oedema (1.2%), flushing (1.1%) and palpitations (0.6%). The low numbers of patient with adverse effects showed lercanidipine had good tolerability in clinical practice.[30]

- The LEAD study in 2003 (n=250) compared the effects of lercanidipine, felodipine and nifedipine GITS, on BP and heart rate, in patients with mild to moderate hypertension. BP decreased significantly and equally in all treatment groups ($p<0.01$). Adverse events were significantly lower in patients treated with nifedipine and lercanidipine than felodipine ($p<0.05$). Overall lercanidipine had the best tolerability profile with a lower incidence of withdrawals from ankle oedema (0.9%), compared to nifedipine GITS (3.8%) and felodipine (4.5%).[31]

- The 2003 ELLE study (n=324) compared the effects of lercanidipine, lacidipine (not licensed in Ireland) and nifedipine GITS on BP and heart rate in elderly hypertensive patients (≥65 years). BP was found to be significantly decreased in all treatment groups ($p<0.01$). Lercanidipine was found to be equivalent to nifedipine and better than lacidipine at lowering BP. Adverse events were lowest in the lercanidipine group (19.4%), compared to lacidipine (27.1%) and nifedipine GITS (28.4%).[32]

- Tolerability of lercanidipine compared to amlodipine and lacidipine was assessed in a 2002 study of elderly hypertensive patients (n=828). While all the drugs had similar antihypertensive effect, the incidence of peripheral oedema in the amlodipine group (19%) was significantly higher compared to the lercanidipine (9.3%) and lacidipine (4.3%) groups ($p<0.001$).[33]

- In 2015 a study of 104 hypertensive patients with cerebral ischaemic stroke compared amlodipine with lercanidipine. There was no statistical difference between the two groups in terms of BP reduction. The lercanidipine group was found to have less adverse events than the amlodipine group (5.7% compared to 19.2%, $p=0.03$). This trial stated that larger studies were required to verify the results.[34]

Felodipine

Felodipine has been less extensively studied than other DHP CCBs such as amlodipine. Two of the most significant trials are the Hypertension Optimal Treatment trial and the STOP-2-Hypertension-2 trial.

- The 1994 Hypertension Optimal Treatment (HOT) trial involved 18,790 patients in 26 countries with hypertension (defined as diastolic BP between 100-115 mmHg). Each patient was randomly assigned to one of three groups, each with a different target diastolic BP. Results showed that taking felodipine daily, reduced BP in all 3 treatment groups. The lowest incidence of cardiovascular events occurred with a diastolic BP of 82.6 mmHg.[35]

- The 1999 STOP-2-Hypertension-2 trial investigated 6,614 elderly patients (aged 70-84 years) with hypertension. Each patient was randomly assigned to one of three treatment groups: conventional antihypertensives (beta-blockers or diuretics), CCBs or ACE inhibitors. There was a similar decrease in BP with each treatment group from baseline values. There was no significant difference between older and newer antihypertensive drugs in the primary combined endpoint of prevention of cardiovascular mortality or major events (p=0.89).[36]

- A 2015 a trial (n=281) which compared lercanidipine with felodipine sustained release, for the treatment of mild to moderate hypertension demonstrated that there was a significant difference in BP lowering with each drug from baseline. The mean systolic BP decreased by 18mmHg in the lercanidipine group and 19mmHg in the felodipine group (p<0.001).[37] There was no significant difference in BP lowering effect between groups. Incidence of adverse events was similar between groups, 26.6% for the lercanidipine group and 25.3% for the felodipine group (p=0.892).[37]

Nifedipine long-acting

The BP lowering efficacy of nifedipine GITS has been demonstrated in the LEAD and ELLE studies, as previously discussed in the lercanidipine section.[31,32]

- The 2000 INSIGHT trial (n=6,321) was a large scale multi-centre trial across Europe and Israel involving patients aged 55-80 years with hypertension and one other cardiovascular risk factor. Patients were randomly assigned to either nifedipine GITS or co-amilozide (amiloride and

hydrochlorothiazide). Following titration, BP in both groups remained close to 138/82mmHg for the duration of the trial. There was no difference in the primary endpoints of cardiovascular death, myocardial infarction (MI), heart failure or stroke between treatment groups (p=0.35). Nifedipine patients had 8% more withdrawals due to peripheral oedema (p<0.0001), but co-amilozide patients had more serious side effects e.g. metabolic disorders.[38]

- Nifedipine GITS was compared with amlodipine in a multi centre RCT (n=155), both drugs were found to significantly reduce BP.[39] Comparison between groups found a similar reduction in mean diastolic BP. This was the primary criterion for assessing efficacy. The incidence of adverse events was low, 7.9% in the amlodipine group and 10.1% in the nifedipine group. Most of the adverse effects were headache, dizziness and vertigo.[39]

Nilvadipine

Nilvadipine has been less extensively studied than other DHP CCBs such as amlodipine and lercanidipine.

- A 1992 trial (n=183) comparing nilvadipine and nitrendipine (not licensed in Ireland) to placebo, found that nilvadipine lowered BP significantly better than placebo and slightly more effectively than nitrendipine. Nilvadipine also had a longer duration of effect due to its half-life of 20 hours, compared to 12 hours for nitrendipine. Common side effects included headache, flushing, palpitations and peripheral oedema.[40]

- A 2005 double-blind prospective RCT comparing nilvadipine to amlodipine (n=168) found that there was no significant difference in BP lowering between the treatment groups (p=0.22). There was also no significant difference in ADRs between the groups (p=0.24).[41] Lower limb oedema accounted for 20% of the ADRs reported in nilvadipine patients and 29.3% in amlodipine patients.[41]

6.1.1.2 Systematic reviews of hypertension

Observational studies, meta-analyses and review articles of CCBs were also considered in the review process. A selection of relevant studies are included in tables 4 and 5 below.

Table 4: Meta-analyses of calcium channel blockers under review

Meta-analysis	Year	Reviewed drugs	Conclusions
Peripheral oedema associated with CCBs; incidence and withdrawal rate[42]	2011	CCBs compared to ACE inhibitors, ARBs, beta-blockers, other CCBs, direct renin inhibitors and thiazides	There was a significant increase in withdrawal rate due to peripheral oedema with CCBs compared to placebo. Incidence of peripheral oedema was 57% lower with lipophilic CCBs than with the traditional DHPs.
Results of a meta-analysis comparing the tolerability of lercanidipine and other DHP CCBs[43]	2009	lercanidipine amlodipine felodipine lacidipine* manidipine* nifedipine	Lercanidipine was associated with a lower risk of treatment withdrawal due to peripheral oedema than the 1st generation DHPs, but not the 2nd generation.
Evidence based evaluation of CCBs for hypertension[44]	2002	CCBs, diuretic or beta-blocker and ACE inhibitors	Mortality and major cardiovascular events with CCBs were similar to those with conventional first line therapy (diuretics and beta-blockers) and ACE inhibitors. CCBs had reduced risk of non-fatal stroke (25%) compared to conventional therapy.
Cardiovascular protection and blood pressure reduction: a meta-analysis[45]	2001	CCBs, ACE inhibitors, diuretics, beta-blockers	All antihypertensive drugs have similar long term efficacy and safety. CCB may be more effective in stroke prevention.

DHP: Dihydropyridine; CCB: Calcium channel blocker; ACE: Angiotensin converting enzyme; ARB: Angiotensin-II receptor blocker
* Not licensed in Ireland

Table 5: Reviews of calcium channel blockers

Review	Year	Reviewed drugs	Conclusions
Time course for BP lowering of DHP CCBs[46]	2014	amlodipine lercanidipine manidipine* nifedipine felodipine	Amlodipine, nifedipine, manidipine,* felodipine and lercanidipine taken once daily, consistently lower BP by a similar amount over 24 hours and significantly more than placebo ($p<0.00001$).
State-of-the-art treatment of hypertension; established and new drugs[47]	2014	CCBs, ACE, ARB diuretics beta-blockers	3rd generation CCBs induce less peripheral oedema than 2nd generation CCBs.
Effects of ACE inhibitors, CCBs and other BP lowering drugs; results of prospectively designed overviews of randomised trials[48]	2000	CCBs, ACE, other BP lowering drugs	Trials comparing CCB vs. placebo showed reductions in stroke and major cardiovascular events of 30-40% in favour of CCBs. CCBs reduced BP by the same amount as diuretic or beta- blocker based therapy.

CCB: Calcium channel blocker; ACE: Angiotensin converting enzyme; ARB: Angiotensin-II receptor blocker
* Not licensed in Ireland

Comparison with other classes of antihypertensives

In 2001 Staessen et al. investigated if antihypertensives have a role in cardiovascular protection beyond BP reduction. A meta-analysis was conducted on nine trials, which included 62,605 patients with isolated systolic hypertension.[45] Results demonstrated that all antihypertensive drugs have similar long-term safety and efficacy. When compared to diuretics and beta-blockers, CCBs and ACE inhibitors provided similar overall protection against cardiovascular complications, but CCBs provided more protection from the risk of stroke (13.5%, p=0.03), and less reduction in the risk of myocardial infarction (19.2%, p=0.01).[45]

Another meta-analysis by Opie and Schall (2002) compared the safety and efficacy of CCBs to conventional therapy (diuretics or beta blockers) or ACE inhibitors.[44] There were six trials included, with 45,933 patients. In the comparison with diuretics and beta-blockers, the CCB group had a reduced risk of non-fatal stroke (25%, p=0.001). Risk of mortality and major cardiovascular events were similar, however the risk of MI, was 18% higher (p=0.013) in the CCB group than in the conventional therapy group. When CCBs were compared to ACE inhibitors there was no difference in total and cardiovascular mortality.[44]

Neal et al. (2000) conducted a review investigating the effects of different classes of antihypertensives on mortality and major cardiovascular morbidity.[48] The analysis included seventeen studies with 75,924 patients. Studies comparing CCBs with a diuretic or beta-blocker based regimen demonstrated there was no difference in BP lowering effect between treatment groups, however there was a significantly lower risk of stroke (13%) and a 12% greater risk of coronary heart disease (of borderline significance) with the CCB groups. Studies of CCBs versus placebo demonstrated a reduction in stroke and major cardiovascular events of 30-40%.[48]

Comparison between dihydropyridine calcium channel blockers

In 2014 a systematic review was carried out to assess the hourly variation in systolic and diastolic BP with DHP CCBs, over a 24 hour period, for at least three weeks. The review included sixteen RCTs (n=2,768), involving five drugs given once a day: amlodipine, lercanidipine, manidipine (not licensed in Ireland), nifedipine and felodipine and one drug given twice daily, nicardipine (not licensed in Ireland). Results found the DHPs studied in this review lowered BP by a similar amount

over a 24 hour period and significantly more than placebo for systolic and diastolic BP ($p<0.00001$).[46]

Evidence of tolerability of calcium channel blockers

The tolerability of lercanidipine compared to other CCBs was assessed by Makarounas-Kirchmann et al. (2009), in a meta-analysis conducted on eight RCTs (n=2,034).[43] Results showed that lercanidipine did not differ statistically from the other CCBs in BP lowering efficacy. However there was a difference in tolerability between the DHPs.[43] Compared to the first generation DHPs, lercanidipine was associated with a reduced relative risk (0.44) of peripheral oedema and a reduced relative risk (0.24) of patients withdrawing from treatment, because of peripheral oedema.[43] There was no significant difference in tolerability between lercanidipine and the second generation CCBs.[43] Peripheral oedema is the commonest side effect reported in DHPs and can contribute to poor adherence to therapy.[33,43]

A meta-analysis by Makani et al. (2011) evaluated the incidence and withdrawal rate due to peripheral oedema with CCBs.[42] One hundred and six studies with 99,469 participants were included in the analysis. Trials compared CCBs with placebo and other antihypertensive therapies. Results found that there was a significant increase in withdrawal rates due to peripheral oedema with CCBs compared to placebo ($p<0.0001$). The risk of peripheral oedema with lipophilic DHPs (e.g. lercanidipine) was 57% lower than traditional DHPs (RR 0.43, $p<0.0001$). The incidence of peripheral oedema with DHPs was 12.3% compared to 3.1% with non DHPs ($p<0.0001$).[42]

A systematic review on the treatment of hypertension stated that the five main classes of antihypertensives i.e. ACE inhibitors, ARBs, diuretics, beta-blockers and CCBs all reduce BP by a similar amount.[47] However the tolerability profile of these classes may differ significantly. Third generation CCBs induce less peripheral oedema in hypertensive patients than second generation CCBs.[47]

Calcium channel blockers have similar efficacy in terms of blood pressure lowering effects. Calcium channel blockers differ in tolerability profiles.

6.1.1.3 Clinical guidelines for hypertension

In the absence of clinical guidelines specific to Ireland, international guidelines for hypertension from the UK, Europe and America were reviewed, to establish if a particular CCB was preferred within the class. The results are shown in table 6.

Table 6: Review of clinical guidelines for hypertension

Review Body	Guideline	Year	Recommendations	Preferred CCB
American College of Cardiology/American Heart Association (ACC/AHA)[49]	An effective approach to high BP control	2014	**HTN Stage 1**: BP systolic 140-159 or diastolic 90-99. Lifestyle modifications and consider adding a thiazide. **HTN Stage 2**: BP systolic >160 or diastolic >100. Lifestyle modification & ➢ thiazide **and** ACE inhibitor, ARB or CCB ➢ or ACE inhibitor **and** CCB	Not specified
European Society of Cardiology and European Society of Hypertension (ESC/ESH)[50]	Guidelines for the management of arterial HTN	2013	CCB, diuretics, beta blockers, ACE inhibitors and ARBs are all suitable for initiation and maintenance of antihypertensive treatment.	Not specified
National Institute for Health and Care Excellence (NICE) and the British Hypertension Society[21]	HTN in adults-diagnosis and management	2011	CCB is used step 1 in management of HTN for >55yrs or black African/Caribbean of any age. CCB can be used second line in combination with an ACE or ARB. Use once daily dosing. Prescribe generically.	Not specified
Scottish Intercollegiate Guideline Network (SIGN)[51]	Guideline number 97-Risk estimation and the prevention of CVD	2007	CCBs are as effective as the other classes of antihypertensive agents. CCBs and thiazide diuretics are most clinically and cost effective choice in the majority of cases.	Not specified

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

These guidelines all recommend that CCBs are used for the treatment of hypertension.[21,49-51] However there are differences between guidelines in relation to the stage that these drugs are introduced in the hypertension treatment algorithm. The jointly issued guidance from the American College of Cardiology and the American Heart Foundation recommends that CCBs are used in the management of stage 2 hypertension.[49] None of the guidelines differentiate between individual calcium channel blockers, assuming a class effect. The joint guidance issued by the European Society of Cardiology and the European Society of Hypertension, states that they are all equally suitable for initiation and maintenance of antihypertensive treatment.[50]

Northern Ireland has recently published a regional formulary to promote safe, clinically effective and cost effective prescribing of medicines.[52] This formulary recommends amlodipine as first choice CCB in the treatment of hypertension.[52] Other NHS trusts in the UK have also selected amlodipine as the first choice of calcium channel blocker, such as NHS Lothian, County Durham and Darlington NHS trust and the Dorset Cardiology working group on hypertension.[53-55]

AMLODIPINE is among the calcium channel blockers recommended for treating hypertension in a number of international clinical guidelines.

AMLODIPINE is the recommended calcium channel blocker in a number of NHS regional formularies.

6.1.2 Angina

6.1.2.1 Clinical efficacy of stable angina

A literature search was carried out to identify the main clinical trials of CCBs used to treat stable angina. The following databases were used: EMBASE (1947-2016), MEDLINE (1946-2016) and CINAHL (1937-2016). Trials examined are outlined in table 7, this list is not exhaustive but represents a number of the most significant trials of CCBs for stable angina. Lercanidipine and nilvadipine are not currently licensed to treat stable angina in Ireland (see table 2).[18,20] The majority of direct drug comparisons in stable angina trials involve calcium channel blockers with beta blockers.[56]

Table 7: Calcium channel blocker trials for stable angina included in this review

Trial	Design	Drugs used in trial	Findings
Amlodipine in stable exertional angina pectoris (1991)[57]	Multi centre, placebo-controlled, double-blind, dose-response study, n=136	**Amlodipine** vs. placebo	There was significant improvement in angina symptoms with amlodipine compared to placebo (p<0.01).
AMSA (2000)[58]	Double blind, RCT, n=127	**Amlodipine** vs. metoprolol SR	There was no significant difference between treatment groups, both significantly reduced the mean number of angina attacks (p=0.001).
CAMELOT (2004)[27]	Multi centre, double-blind, RCT n=1,991	**Amlodipine**, enalapril or placebo	The primary endpoint was adverse cardiovascular events including hospitalisation for angina. This was significantly reduced in the amlodipine group compared to placebo (p<0.002) and compared to the enalapril group (p<0.003).
IMAGE (1995)[59]	Multi centre, double-blind, parallel group4 n=280	Metoprolol vs. **nifedipine SR**	Nifedipine SR and metoprolol prolonged exercise tolerance from baseline. Metoprolol was significantly more effective than nifedipine SR (p<0.05).
TIBBS (1995)[60]	Multi centre, double-blind, RCT n=330	Bisoprolol vs. **nifedipine** SR	Reductions in ischaemic episodes occurred with both drugs. Bisoprolol was significantly more effective than nifedipine (p<0.0001).
TIBET (1996)[61]	Double blind, parallel group, RCT n=608	Atenolol vs. **nifedipine** SR vs. combination	Atenolol, nifedipine and their combination significantly and equally reduced reversible ischaemia during exercise and ambulatory monitoring.
ACTION (2004)[62]	Multi centre, double blind, RCT n=7,665	**Nifedipine** GITS vs. placebo	No effect on primary endpoint of major cardiovascular event-free survival was found with when nifedipine GITS was added to existing angina therapy. Nifedipine GITS significantly reduced secondary endpoints of death, cardiovascular event or cardiovascular procedure compared to placebo (p=0.0012)
The effect of treatment with felodipine as a single agent in coronary artery disease (1989)[63]	Double blind, crossover, n=25	**Felodipine** vs. placebo	Felodipine caused a 10% increase in median exercise time after 2 weeks (p<0.05) and 7% at 4 weeks (not significant). Felodipine has shown anti-anginal effects, which may be more limited than other related drugs.
Felodipine and amlodipine in stable angina (1997)[64]	Double blind, crossover, RCT n=52	**Felodipine** vs. **amlodipine**	There was a significant reduction is anginal attacks with both drugs compared to baseline (p<0.001). There was no significant difference between drugs.
TRAFFIC (1999)[65]	Multi centre, parallel group, RCT n=397	**Felodipine** vs. metoprolol vs. **felodipine**-metoprolol	Felodipine (p=0.03) and felodipine–metoprolol (p=0.04) significantly increased exercise duration compared to metoprolol alone.

SR: Slow- release; RCT: Randomised controlled trial

Key findings from clinical efficacy in stable angina:

Amlodipine

Taylor et al. (1991) demonstrated the efficacy of amlodipine in the treatment of stable angina. A significant ($p<0.01$) improvement in exercise duration was seen with amlodipine treatment compared to placebo.[57] Midtbø and Mølstad (2000) also demonstrated a significant reduction in angina attacks with amlodipine ($p=0.001$).[58] In this trial amlodipine and metoprolol were compared and found to be equally effective in treating stable angina.[58] In the CAMELOT trial (2004) amlodipine was compared with an ACE inhibitor (enalapril) or placebo.[27] Primary endpoints included hospitalisation for angina. Amlodipine was found to have significantly less episodes of hospitalisation for angina than enalapril ($p=0.03$) or placebo ($p=0.02$).[27]

Amlodipine and felodipine were compared in a trial by Koenig et al. (1997).[64] Both drugs significantly ($p<0.001$) decreased the number of angina attacks and ischaemic episodes.[64] There was no significant difference found in efficacy between the drugs. However cardiovascular endpoints were not assessed in this trial and the study was limited by small sample size ($n=52$).

Nifedipine long-acting

The efficacy of nifedipine long-acting in stable angina has been demonstrated in the TIBBS (1995) and TIBET (1996) trials.[60,61] In the TIBBS trial nifedipine SR was compared with bisoprolol. Both drugs were effective in reducing the number and duration of ischaemic episodes in patients with stable angina. However bisoprolol was found to be significantly more effective than nifedipine SR ($p<0.0001$).[60] In the TIBET trial nifedipine SR was compared with atenolol. Both were found to be equally effective in reducing markers of reversible ischaemia during exercise and ambulatory monitoring.[61] The IMAGE trial (1995) compared nifedipine SR with metoprolol and found metoprolol was significantly more effective in prolonging exercise tolerance in patients with stable angina ($p<0.05$).[59] The ACTION trial (2004) demonstrated nifedipine GITS could be used safely in the treatment of stable angina, as it prolongs cardiovascular event and procedure-free survival ($p=0.0012$).[62]

Felodipine

There are fewer trials to provide evidence of efficacy of felodipine in the treatment of stable angina. A small early trial by Metcalfe et al. (1989) showed that felodipine had antianginal effects, however the significance of this effect was found to reduce at 4 weeks treatment.[63] The larger TRAFFIC trial (1999) demonstrated that felodipine was an effective antianginal drug.[65] It was found to be significantly better than metoprolol when used as monotherapy (p=0.03), and also significantly better in combination with metoprolol compared to metoprolol monotherapy (p=0.04).[65]

6.1.2.2 Systematic reviews of stable angina

Relevant meta-analyses and reviews for the treatment of stable angina with CCBs were also considered in the review process. A selection of relevant studies are included in table 8 below:

Table 8: Meta-analyses and reviews of CCBs in stable angina

Meta-analysis/Review	Year	Reviewed drugs	Conclusions
Treatment of stable angina[66]	2007	Beta blockers CCBs Nitrates	Symptoms of chronic stable angina can usually be managed with optimum doses of CCB, beta blocker or long-acting nitrate, alone or in combination
Current status of safety and efficacy of CCBs in cardiovascular diseases: A critical analysis 100 studies[67]	2000	CCBs	Evidence based on RCTs suggest equivalent safety of CCBs (other than short-acting nifedipine) and beta blockers in stable angina
Meta-analysis of trials comparing beta blockers, CCBs, and nitrates for stable angina 90 studies[56]	1999	Beta blockers CCBs Long-acting nitrates	RCTs of stable angina show that beta blockers provide similar clinical outcomes and fewer adverse effects than CCBs

CCB: Calcium channel blocker

The most significant meta-analysis of CCBs was carried out by Heidenreich et al. (1999).[56] This analysed 90 studies, comparing the relative tolerability and efficacy of all classes of CCBs with beta blockers and nitrates in the treatment of stable angina. There was no significant difference found with angina episodes, nitroglycerin use and exercise time between CCBs and beta blockers.[56] When DHP CCBs were compared to beta blockers separately there were fewer adverse events (odds ratio, 0.63) and angina episodes per week (odds ratio, 0.61) with beta blockers than CCBs.[56] In this meta-analysis nifedipine accounted for 79% of all the DHPs analysed therefore it is difficult to demonstrate if the increase in adverse events is a class effect.[56] The meta-analysis concluded that

as beta blockers were better tolerated than CCBs, they should be considered first line in stable angina.[56]

A critical analysis of the safety and efficacy of all CCBs in cardiovascular diseases by Opie at al. (2000) showed that there was a lack of large RCTs comparing CCBs to beta blockers in stable angina.[67] From the evidence available from RCTs, beta blockers and CCBs are thought to have equivalent safety and efficacy in stable angina.[67] The review concluded that more RCTs with open label follow up and prospective observational studies are required on CCB safety.[67]

A review of the treatment of stable angina by Ben-Dor and Battler (2007) stated that the three major classes of anti-ischaemia drugs: CCBs, beta blockers and nitrates; have been shown to decrease the frequency of angina and prolong the duration of exercise before the onset of angina.[66] Head-to-head comparative trials have failed to demonstrate greater antianginal efficacy for any one class of drugs over another. No observed differences have been found between rates of cardiac death or MI between beta blockers and CCBs.[66]

Calcium channel blockers reviewed have similar efficacy in treating stable angina.
Calcium channel blockers and/or beta blockers can be used to treat stable angina.

6.1.2.3 Clinical guidelines for stable angina

International guidelines for stable angina from the UK, Europe and America were reviewed, to establish if a particular CCB was preferred within the class. International guidelines included rate-limiting CCBs (verapamil and diltiazem), which are beyond the scope of this document. The results are shown in table 9.

Table 9: Review of clinical guidelines for stable angina

Review Body	Guideline	Year	Recommendations	Preferred CCB
European Society of Cardiology (ESC)[68]	Guidelines on the management of stable coronary artery disease	2013	First line: CCB or beta blocker to control heart rate and symptoms	Not specified
National Institute for Health and Care Excellence (NICE)[69]	Stable angina management (CG126)	2011	First line: CCB or beta blocker	Not specified
Scottish Intercollegiate Guideline Network (SIGN)[70]	Guideline number 96- Management of stable angina	2007	First line: Beta blocker Add CCB to beta blocker if symptom control not achieved. Use rate-limiting CCB (verapamil or diltiazem), long acting nitrate or nicorandil if intolerant to beta blocker.	DHP CCB if added to beta blocker. Amlodipine or felodipine if coexisting heart failure.
American college of cardiology/ American heart association (ACC/AHA)[71]	Guidelines for the management of patients with chronic stable angina	2002 (updated 2007)	Beta-blocker should be used, substitute with a CCB if contraindicated or add in CCB.	Not specified

The ESC and NICE guidelines recommend that either a beta blocker or CCB could be used first line in the treatment of stable angina.[68,69] The SIGN and joint ACC/AHA guidelines both recommend that a beta blocker is used first line and a CCB added if symptom control is not achieved.[70,71] These guidelines also recommend that if there is intolerance to a beta blocker it can be substituted with a CCB.[70,71] The SIGN guideline states that rate-limiting CCBs (verapamil or diltiazem) can be used alone as an alternative to a beta blocker, however if a CCB is added to a beta blocker then the DHP CCBs are more suitable.[70] There is no specific CCB chosen by the ESC, NICE or the ACC/AHA guidelines.[68,69,71] Amlodipine and felodipine are the most appropriate CCBs for addition to beta blocker therapy in heart failure.[70]

The Northern Irish formulary and the NHS Lothian formulary recommend amlodipine for patients with angina, who are already taking a beta blocker and diltiazem for patients who cannot tolerate a beta blocker.[52,53]

Calcium channel blockers or beta blockers are recommended for the treatment of stable angina in international clinical guidelines.
Amlodipine is the CCB of choice if added to a beta blocker to treat stable angina.

Refer to the MMP preferred drug review for beta blockers for further information on the use of beta blockers in stable angina.[72]

6.2 Patient factors

6.2.1 Dosing and administration

The DHP CCBs considered in this review are taken once daily, with the exception of nifedipine SR, which is taken twice daily (table 10).[15-20] It has been found that reducing dosage frequency from multiple daily dosing to once daily dosing may improve adherence to therapies among patients.[73] A Cochrane review on improving adherence to treatment in patients with high BP found that reducing the number of daily doses was effective in increasing adherence to BP lowering medication.[74] NICE guidance on hypertension also recommends once daily dosing.[21]

Table 10: Dosing regimen for calcium channel blockers[15-20]

CCB	Dose for HTN and angina	Frequency	Administration
Amlodipine	HTN and angina: 5mg (max 10mg daily)	once daily	swallow whole, with a small amount of water, before or after food.
Felodipine	HTN: 5mg (max 10mg daily) Angina: 5mg (range 2.5mg-10mg daily)	once daily	swallow whole with water in the morning. Take without food or following a meal not rich in fat or carbohydrate.
Nilvadipine	HTN: 8mg (max 16mg daily)	once daily	swallow whole with a small amount of liquid in the morning, after breakfast.
Lercanidipine	HTN: 10mg (max 20mg daily)	once daily	swallow whole with water. Take 15 minutes before meals, preferably breakfast.
Nifedipine SR	HTN and angina: 10-20mg (max 40mg daily)	twice daily	swallow whole with a small amount of liquid, irrespective of meal times.
Nifedipine GITS	HTN: 20-30mg Angina: 30mg (max 90mg daily)	once daily	swallow whole with a small amount of liquid, irrespective of meal times. **Must not** be chewed, bitten or broken up.

HTN: Hypertension; SR: Slow- release; GITS: Gastrointestinal therapeutic system

CCBs should be swallowed whole, with a small amount of liquid. Amlodipine and nifedipine long-acting can be taken at any time of day, irrespective of meals.[15,16,19] Due to the formulation of Nifedipine GITS, it must not be chewed, bitten or broken-up.[15] Felodipine should be taken on an empty stomach, or following a meal not rich in fat or carbohydrate.[17] In contrast nilvadipine should not be taken on an empty stomach as it can decrease bioavailability.[18] Lercanidipine should be taken 15 minutes before meals, because the bioavailability of lercanidipine increases four fold when it is ingested up to 2 hours after a high fat meal.[20]

AMLODIPINE is the calcium channel blocker of choice with regards dosing and administration.

6.3 Cautions and contraindications

Table 11 lists the cautions and contraindications common to the DHP CCBs.[2] A complete list for each drug can be found in the individual summary of product characteristics (SmPC).[15-20]

Table 11: Cautions and contraindications for calcium channel blockers[2]

Cautions	Contraindications
Left ventricular dysfunction	Cardiogenic shock
Withdraw if existing chest pain worsens	Significant aortic stenosis
Withdraw if ischaemic pain develops after initiating.	Uncontrolled heart failure
Severe hepatic impairment	Unstable angina- within one month of MI
Severe renal insufficiency	Dantrolene infusion-risk of ventricular fibrillation

6.4 Adverse drug reactions (ADRs)

The DHP CCBs have ADRs in common due to their pharmacological profile i.e. vasodilatory properties; these include headache, dizziness, flushing and peripheral oedema.[75] Although these ADRs occur with all the DHP CCBs, the differences in the pharmacodynamic and pharmacokinetic profiles of each drug affects the incidence with which they occur.[13] ADRs can be classified according to the reported frequency of occurrence (table 12).

Table 12: Description of the frequency of adverse drug reactions[2]

Type of adverse drug reaction	Frequency of adverse drug reaction (per administration of the drug)
Very common	≥ 1 in 10
Common	≥ 1/100 to < 1 in 10
Uncommon	≥ 1/1000 to <1/100

The common/very common ADRs for CCBs are listed in table 13. A full list of ADRs for each drug can be found in the individual SmPC.[15-20] This table demonstrates that ADRs are seen more frequently with nifedipine and amlodipine. Lercanidipine does not have any very common or common ADRs, it does however have uncommon ADRs. These are dizziness, flushing, headache, tachycardia, palpitations and peripheral oedema.[20] Despite these ADRs the DHP CCBs are widely used in hypertension as they are considered potent, well tolerated and safe.[76] Borghi et al. (2003) found that the most frequently reported adverse effects in patients taking DHP CCBS was peripheral

oedema (13.6%), headache (5.8%), flushing (3.9%) and rash (2%).[77] Switching these patients to lercanidipine showed significant reductions in these adverse effects ($p<0.001$).[77]

Table 13: Common/very common adverse drug reactions of calcium channel blockers[15-20]

Adverse Drug Reaction	Amlodipine	Nifedipine	Felodipine	Nilvadipine	Lercanidipine
Dizziness	✓			✓	
Flushing	✓		✓	✓	
Headache	✓	✓	✓	✓	
Peripheral Oedema	✓✓	✓	✓✓	✓	
Vasodilation		✓			
Palpitations	✓				
Dyspnoea	✓				
GI Disturbance, altered bowel habit	✓				
Constipation		✓			
Malaise		✓			
Visual disturbance	✓				
Muscle cramps	✓				
Fatigue/asthenia	✓				
Somnolence	✓				

✓ common adverse-effect; ✓✓ very common adverse-effect

Peripheral oedema

Oedema is an accumulation of fluid in the interstitial space which occurs as the capillary filtration exceeds the limits of lymphatic drainage.[78] Peripheral oedema refers to fluid accumulation in a limb or limbs, most commonly lower.[79] There are many different causes of peripheral oedema such as: allergic reaction, cardiac disease, cellulitis, DVT and lymphedema.[78] Peripheral oedema is also an adverse effect of certain medications including CCBs.[78]

The exact mechanism that causes peripheral oedema in DHP CCBs is unclear, it is not linked to systemic retention of fluid and does not respond to diuretics.[6] It is thought to be due to an increase in intracapillary hydrostatic pressure which causes an increase in fluid filtration from the vascular to the interstitial compartment.[33] Theories to explain the less frequent occurrence of peripheral oedema with the third generation lipophilic CCBs include; that there is less sympathetic activation and therefore less difference between arteriolar and venular dilation, or that there is less effect on vascular permeability and therefore fluid extravastation.[5,31,33]

Although peripheral oedema is not life-threatening it can cause distress to the patient and lead to decreased compliance.[76] The incidence of peripheral oedema with the DHP CCBs has been

investigated in a meta-analysis of one hundred and six studies by Makani et al. (2011).[42] This analysis found that the incidence of peripheral oedema was significantly higher (12.3%, p<0.00001) with DHPs, than non DHP CCBs (3.1%).[42] Only 2.4% of patients on DHP CCBs withdrew from treatment due to this ADR.[42]

Patients who experience ADRs but are well controlled with a DHP CCB, may benefit from changing to a lipophilic DHP CCB, such as lercanidipine.[5]

Peripheral oedema is an adverse effect of dihydropyridine calcium channel blockers, it does not respond to diuretics.
Lercanidipine may be used as an alternative in patients with this adverse-effect.

6.5 Drug interactions

The DHP CCBs exhibit a class effect as substrates for the cytochrome P450 isoenzyme CYP3A4. Concomitant use of CCBs and drugs which induce or inhibit this isoenzyme should either be avoided, or the drug taken with caution and appropriate monitoring.[2] Examples of common drugs which induce or inhibit CYP3A4 are listed in table 14.[80] Drugs which are enzyme inhibitors have the potential to reduce the metabolism of CCBs, causing accumulation in the body. Conversely drugs which act as enzyme inducers have the potential to increase metabolism of CCBs, reducing levels of the drug in the body.[80]

Table 14: Drugs which are known to induce or inhibit CYP3A4[80]*

Inhibitors	Inducers
Cimetidine	Carbamazepine
Clarithromycin	Phenobarbital
Diltiazem	Rifampicin
Erythromycin	Phenytoin
Fluconazole	St Johns Wort
Itraconazole	
Ketoconazole	
Ritonavir	
Verapamil	
Grapefruit Juice	

*this list is not exhaustive and is intended to serve as an example only

The DHP CCBs also exhibit drug interactions which are not related to cytochrome P450. The most significant are summarised, a complete list of CCB drug interactions is available in the individual SmPCs and in the British National Formulary (BNF).[2, 15-20]

Beta-blockers: There is an enhanced hypotensive effect when CCBs are given with beta-blockers, therefore care should be taken when they are used together. Nifedipine may cause severe hypotension and heart failure when administered with a beta-blocker, this combination should be avoided.[2,15,16]

Alpha-blockers: There is an enhanced hypotensive effect when CCBs are administered with alpha-blockers. These drugs should only be used together with caution.[2]

Aminophylline/theophylline: CCBs may increase the plasma concentration of aminophylline and theophylline. Patients should be monitored for signs of aminophylline/theophylline toxicity including headache, nausea and tremor and the dose adjusted accordingly.[2, 15-20]

Tacrolimus: The concentration of tacrolimus is increased with amlodipine, felodipine and nifedipine, there is limited evidence with nilvadipine but it is predicted to act similarly. Tacrolimus blood levels should be monitored and the dose adjusted as required.[2, 77]

Ciclosporin: The levels of ciclosporin should be monitored when co-administered with CCBs. Nilvadipine can cause an increase in ciclosporin levels, conversely the concentration of nifedipine can be increased when administered with ciclosporin.[15,16,18] When lercanidipine is co-administered with ciclosporin the levels of both drugs can be increased, this combination should be avoided.[20]

Simvastatin: There is an increased risk of myopathy when high dose simvastatin is co-administered with amlodipine. When amlodipine 10mg was administered with simvastatin 80mg there was a 77% increase in simvastatin levels. Therefore it is advised that amlodipine patients are limited to a dose of 20mg simvastatin.[19] In clinical practice simvastatin 80mg is only recommended in patients with severe hypercholesterolemia and high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks.[81]

Digoxin: Levels of digoxin should be monitored when administered with lercanidipine, nifedipine and nilvadipine, due to the potential increase in plasma concentration of digoxin.[15,16,18,20]

Calcium channel blockers exhibit a class-effect for the majority of drug interactions.

6.6 Cost

Value for money is an important consideration when choosing a preferred CCB. A drug of lower acquisition cost is preferred unless the more expensive has a proven advantage in terms of either safety or efficacy.[82] Cost is also an important consideration for patients who pay for their medicines. Figure 1 below illustrates the price comparison between all the CCBs currently available on the Irish market.[11] This price is based on the typical reimbursement cost per month based on the defined daily dose (DDD) (table 15). The DDD is listed by the World Health Organisation (WHO) collaborating centre for drug statistics methodology and it is by this method that the price of each individual CCB is compared.[12]

Table 15: The defined daily dose for each calcium channel blocker[12]

Drug	Defined daily dose(DDD)
Amlodipine	5mg
Felodipine	5mg
Lercanidipine	10mg
Nifedipine	30mg
Nilvadipine	8mg

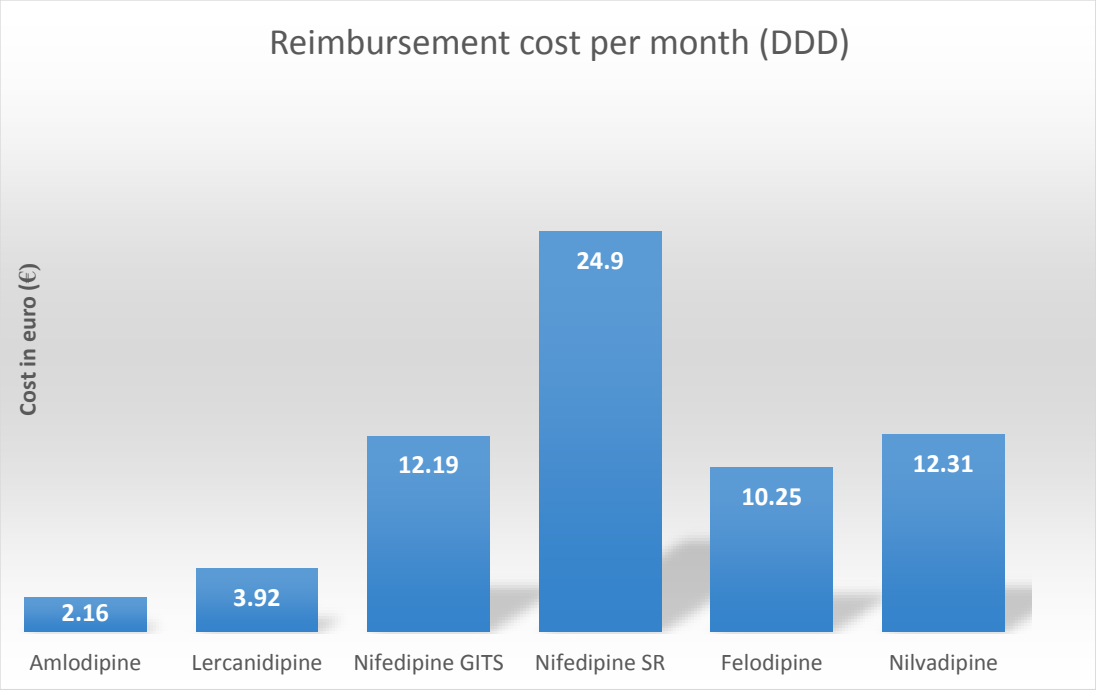

Figure 1: Reimbursement cost per month (28 days), exclusive of pharmacist fees and mark-up, of available CCBs based on the defined daily dose (DDD).
(Costs are correct as of March 2016)

Amlodipine has the lowest reimbursement cost per month, with lercanidipine only slightly more expensive. The low cost for amlodipine and lercanidipine is due to the availability of generics, which are subject to reference pricing by the HSE Corporate Pharmaceutical Unit (CPU). Generics are not available for felodipine, nifedipine long-acting and nilvadipine and therefore these have not been reference priced.

AMLODIPINE is the calcium channel blocker of choice with regards cost.

6.7 Prescribing trends in Ireland

In Ireland the most commonly prescribed DHP CCB is currently amlodipine, accounting for 63% (number of prescription items) of the DHP CCBs prescribed in the General Medical Scheme, between October 2014 and October 2015.[83] The next most frequently prescribed drug in this group is lercanidipine, accounting for 32% (number of prescription items) of the DHP CCBs prescribed during the same 12 month period (see figure 2).

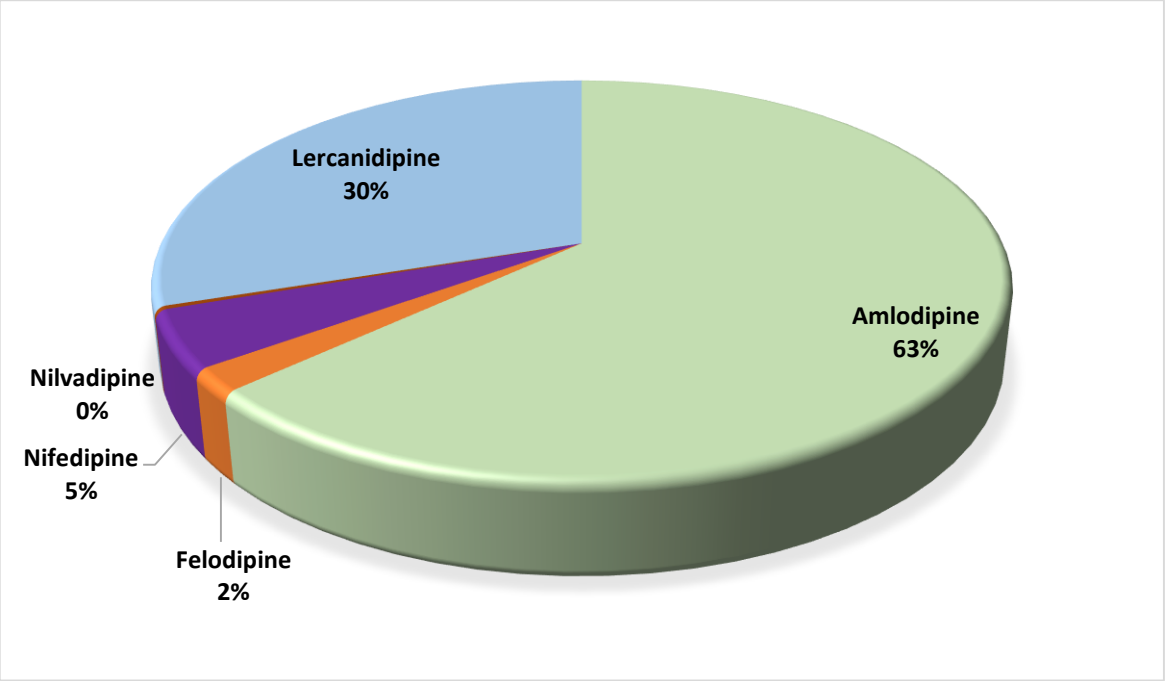

Figure 2: Market share of calcium channel blockers, per number of prescriptions (GMS) Oct 2014 - Oct 2015.

AMLODIPINE is the dihydropyridine calcium channel blocker of choice in terms of national prescribing trends and market share.

7. Summary

AMLODIPINE is the preferred calcium channel blocker for the treatment of hypertension and stable angina under MMP guidance.

- ✓ **Amlodipine is licensed to treat both hypertension and stable angina**
- ✓ **Amlodipine has similar efficacy to other CCBs in terms of reducing blood pressure and treating stable angina**
- ✓ **Amlodipine is among CCBs recommended to treat hypertension in international guidelines**
- ✓ **CCBs or beta blockers are recommended first line to treat stable angina in international clinical guidelines**
- ✓ **Amlodipine is the CCB of choice for hypertension in NHS regional formularies**
- ✓ **Amlodipine is the CCB of choice, in addition to a beta blocker, for stable angina in NHS regional formularies**
- ✓ **Amlodipine has once daily dosing**
- ✓ **Amlodipine has the lowest acquisition cost**
- ✓ **Amlodipine currently holds 63% of the market share in Ireland**

- ✓ **Lercanidipine may be used as an alternative in patients who develop the adverse drug reaction of peripheral oedema**

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Preferred Drugs
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MEDICINES MANAGEMENT PROGRAMME

Appendix A

Prescribing Tips for Amlodipine in Hypertension and Stable Angina

A range of amlodipine preparations are available. Different salts are interchangeable (e.g. besilate, maleate). An up-to-date listing is available on the Health Products Regulatory Authority (HPRA) website at www.hpra.ie.

Therapeutic Indications

- Hypertension
- Chronic stable angina
- Vasospastic (Prinzmetal's) angina

Hypertension and Stable Angina: Dosing and Administration

Full prescribing information is available in the Summary of Product Characteristics (SmPC) which may be accessed freely online at www.hpra.ie or www.medicines.ie. Please consult the SmPC for guidance on prescribing in special patient populations e.g. renal or hepatic impairment.

Table 1: Dosing and administration of amlodipine in hypertension and stable angina

Hypertension and stable angina	Starting dose	Maximum daily dose
Adults	5mg once daily	Increase up to a maximum of 10mg daily
Elderly (>65 years)	Dose as per adults, increase dose with care	

MONITOR

- ✓ **Blood pressure**
- ✓ **Adverse Drug Reactions (ADRs):** Peripheral oedema, headache, dizziness, fatigue, flushing, nausea, abdominal pain and sleep disturbance.*

➢ Peripheral oedema caused by calcium channel blockers does not respond to diuretics. Patients who experience peripheral oedema while taking amlodipine may benefit from switching to **lercanidipine.**

* A full list of adverse-effects is available in the SmPC.

TARGET FOR BLOOD PRESSURE LOWERING

- ✓ In most patients the **target systolic blood pressure is <140mmHg**. A **diastolic blood pressure target of <90mmHg** is generally recommended, except in patients with **diabetes** in whom values **<85mmHg** are recommended.
- ✓ In patients **≥80 years old** the target is **<150/90mmHg.**

Further advice on blood pressure targets including specific populations is available from NICE at www.NICE.org.uk and through the ESC website at www.escardio.org.

CONTRAINDICATIONS

- Cardiogenic shock
- Significant aortic stenosis
- Unstable angina
- Severe hypotension
- Unstable heart failure
- Obstruction of outflow to the left ventricle

CAUTIONS

- Heart failure: ↑ risk of pulmonary oedema
- Hepatic impairment: initiate at low dose
- Renal impairment: normal dose recommended
- Elderly patients: ↑ dose with caution

INTERACTIONS*

- **Strong/moderate inhibitors of CYP3A4:** concomitant use may ↑ levels of amlodipine causing ↑ side effects e.g. azole antifungals (itraconazole), macrolide antibiotics (erythromycin, clarithromycin) and protease inhibitors (ritonavir). Monitor and ↓ dose of amlodipine if required.
- **Inducers of CYP3A4:** concomitant use may ↓ effects of amlodipine e.g. phenytoin, carbamazepine and rifampicin. Monitor and ↑ dose of amlodipine if required.
- **Antihypertensives:** enhanced hypotensive effect, ↑ risk of first dose hypotension with alpha-blockers.
- **Simvastatin:** concomitant use may ↑ levels of simvastatin, ↑ risk of myopathy. Maximum of 20mg simvastatin daily should be administered with amlodipine.
- **Grapefruit juice:** not recommended, may ↑ effect of amlodipine.

*a full list of interactions can be found in the SmPC for amlodipine and Stockley's drug interactions 11th edition.

References: SmPc Istin® 5mg tablets, BNF 71 March-September 2016, Stockley's drug interactions 11th edition March 2016.

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