# How do amlodipine and felodipine compare for the treatment of hypertension or prophylaxis of stable angina?

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## Summary

* For hypertension, limited data suggests that amlodipine has similar or slightly greater efficacy as an antihypertensive when compared with felodipine m/r at comparable doses. However, clinical studies comparing amlodipine with felodipine m/r in hypertension are fairly small with relatively short durations.
* There are few comparative clinical studies between amlodipine and felodipine in the treatment of stable angina. Two prospective comparison studies have shown a more favourable effect on exercise tolerance for daily felodipine m/r 10mg compared to daily amlodipine 10mg, whilst one prospective comparison study concluded that both agents (5mg daily) were equally effective. However, these trials were conducted in a very small number of patients and were of short durations.
* With respect to drug interactions, amlodipine can interact with simvastatin leading to increased risk of myopathy and rhabdomyolysis. The maximum daily dose of simvastatin should therefore not exceed 20 mg when co-administered with amlodipine. There are no restrictions for co-administration of the other statins (atorvastatin, fluvastatin, pravastatin or rosuvastatin) with amlodipine. There is currently no evidence to suggest that felodipine interacts with any of the statins.
* Published data on switching between amlodipine and felodipine in patients with hypertension or angina are limited to a few retrospective observational studies. Patients were switched from amlodipine to felodipine on a milligram-per-milligram basis. Overall, the studies showed similar effect on blood pressure, except one study which showed a significant reduction in blood pressure. Monitor for adverse effects and response.
* The decision on whether to choose amlodipine or felodipine m/r depends on a number of issues that will include local prescribing initiatives and cost, as well as efficacy, tolerability and potential drug interactions. It is important to monitor and regularly review new patients taking either drug for measures of efficacy, tolerability and safety.

Related UKMi documents

* [What are the reported incidences of ankle oedema with different calcium channel blockers?](https://www.sps.nhs.uk/articles/what-are-the-reported-incidences-of-ankle-oedema-with-different-calcium-channel-blockers/)
* [How should ankle oedema caused by calcium channel blockers be treated?](https://www.sps.nhs.uk/articles/how-should-ankle-oedema-caused-by-calcium-channel-blockers-be-treated/)

## Background

Amlodipine and felodipine are dihydropyridine calcium channel blockers. The half-life of amlodipine is reported as 35 – 50 hours, which is consistent with once daily dosing. (1) Felodipine, in the modified release (m/r) formulation has an elimination half-life of approximately 25 hours, which is also consistent with once daily dosing. (2)

Amlodipine has a number of licensed indications. It can be used to treat hypertension, often in combination with a thiazide diuretic, angiotensin II receptor blocker, alpha blocker, beta blocker or an ACE inhibitor. (1) Amlodipine is also licensed for the prophylaxis of stable angina pectoris and is used either as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta-blockers. Amlodipine can also be used for Prinzmetal's (variant or vasospastic) angina when diagnosed by a cardiologist. It is contraindicated in patients with unstable angina, shock or haemodynamically unstable heart failure after acute myocardial infarction. (1;3)

Felodipine m/r is currently licensed for the management of hypertension and the prophylaxis of stable angina pectoris. Felodipine can be used in combination with beta-blockers, ACE inhibitors or diuretics. Felodipine is contraindicated in patients with uncontrolled heart failure or unstable angina. (2;3) It should be used with caution in patients with severe left ventricular dysfunction. (3) There are no significant pharmacological differences between the effects of amlodipine and felodipine on heart rate, myocardial contractility, cardiac output, or peripheral vascular resistance. (4)

This Medicines Q&A aims to review the data available to assist decision-making when choosing and switching between the two agents for hypertension or prophylaxis of stable angina.

## Answer

**Hypertension**

Prospective comparisons of different drug classes have shown that differences in blood pressure (BP) control, rather than differences between drug classes, have the over-riding influence on overall outcome. (5) The BP response to dihydropyridine calcium antagonists is less dependent on patient factors such as age and race compared with other antihypertensive agents such as ACE inhibitors. (6) Current advice from [NICE](https://www.nice.org.uk/guidance/ng136) recommends calcium channel blockers as first line agents in older patients (over 55 years) or black people of African or Caribbean family origin of any age who do not have type 2 diabetes and as potential second line adjunctive agent in younger non-black patients. No specific calcium channel blocker is recommended by [NICE](https://www.nice.org.uk/guidance/ng136). (7) The choice of calcium channel blocker may depend on local recommendations, with the least expensive one being preferred. (8) For patients with both hypertension and angina, amlodipine or felodipine are suitable choices. (8)

**Pharmacokinetic studies/data**

An open label, crossover, pharmacokinetic study conducted in 1997 compared the pharmacokinetic profiles of amlodipine 5mg and felodipine m/r 5mg daily in 28 hypertensive patients (diastolic blood pressure (DBP) between 95 and 115mmHg on two consecutive visits to a hypertension clinic). (9) Patients were given a single dose of the first test drug on day 1 of week 1. The drug was then administered daily for 2 weeks. Following a 2-week placebo washout period the regimen was repeated for the other test drug. Blood samples for drug levels were taken and the effect on BP was measured for 96 hours as a secondary parameter. When comparing the two drugs after a single dose and at steady state (after 2 weeks), no significant differences were found between them with respect to changes in systolic or diastolic blood pressure. It was found that the inter-patient variability in the drug plasma concentration was less with amlodipine than felodipine m/r. Similarly the peak-to-trough plasma concentration ratio was more favourable for amlodipine compared to felodipine m/r. It was not established whether these characteristics reflected ‘smoother and more consistent’ BP control. (9)

**Summary of clinical studies/data**

A number of clinical studies have compared the use of once daily amlodipine 5-10mg and felodipine m/r 5-10mg in mild to moderate hypertension. (10-19) The main studies which were of multi-centre, double blind and double dummy design are summarised in table 1 below. Overall, the trial durations were relatively short compared to how the products would be used in a clinical setting. Several trials were relatively small (n= 48 to 118) or lacked power to detect differences in outcome measures (12;13;15;17-19), while some included only patients of specific ethnicities (11;17;19) so may not be representative of the general population. The primary efficacy measures also varied between the trials.

Based on the limited data available, amlodipine 5-10mg may be associated with a similar or slightly higher response rate (i.e. normalisation of BP) (10-18) and better control of BP following missed doses compared with felodipine m/r 5-10mg (10;17). In addition, amlodipine seemed to be tolerated as well as, or in some studies, better than felodipine m/r. (12;13;16)

## Table 1: Summary of published clinical trials comparing amlodipine and felodipine m/r for hypertension

| **Patient population** | Study Design | **Drug & Dose** | **Basic Results** |
| --- | --- | --- | --- |
| Hypertension (DBP 95 – 114 mmHg).Patients aged 18-75 years (n=193). (13) | Multicentre, randomised, double blind parallel-group study with a 4-week washout phase preceding the active phase.The primary efficacy endpoint was to determine whether treatment was successful (defined as ‘patient responded with DBP ≤90mmHg or a decrease of at least 10mmHg from baseline, with no serious/severe adverse events’) or unsuccessful (defined as ‘patient did not respond or had serious/severe adverse events’). | Treatment: Monotherapy with amlodipine 5mg (n=101) vs. felodipine m/r 5mg (n=92) for 12 weeks. The dose was doubled to 10mg if after 4 or 8 weeks of treatment the DBP was ≥95mmHg. \*If the DBP was still ≥90mmHg after 4 weeks of 10mg therapy, the dose was halved and lisinopril 5mg added. | No significant difference in efficacy between the two groups was seen. More patients on amlodipine (68%) met pre-determined BP lowering target than those on felodipine m/r (53%).A greater number of patients on felodipine m/r (42%) reported adverse events than on amlodipine (33%) and the between-group difference in the rate of severe adverse events was statistically significant but the between-group difference in withdrawal due to adverse events was not statistically significant. No power calculation was carried out.  |
| Elderly patients with primary hypertension (DBP 90 – 115 mmHg).Patients aged over 65 years (n=534). (14) | Multicentre, double blind, double dummy, parallel group study with 3-week placebo washout phase.The primary objective was to compare the tolerability of felodipine m/r with amlodipine in elderly patients with hypertension.  | Treatment: Monotherapy with felodipine m/r 2.5mg (n=265) vs. amlodipine 5mg (n=269) for 9 weeks. Patients were reassessed after 3 and 6 weeks, and doses were increased to felodipine 5mg then 10mg or amlodipine 10mg if BP remained above 160/90 mmHg. | Vasodilatory adverse events were reported by 32% of felodipine m/r patients and 43% of amlodipine patients. (p=0.007).Both drugs provided effective control of BP though amlodipine may have produced slightly greater mean reductions in both SBP and DBP which may be due to patients receiving a higher average daily dose of amlodipine (7.3mg) when compared to felodipine m/r (5.5mg). This may also explain the higher frequency of vasodilatory adverse events in the amlodipine group.  |
| Hypertension (DBP 95 – 115 mmHg) (n=118). (15) | Multicentre, randomised, double blind, double dummy, parallel group study preceded by 2-week drug free and 2-week placebo washout phases.The objective was to compare the efficacies in lowering BP, response rates 24 hours after dose and tolerability of the two drugs.  | Treatment: Monotherapy with felodipine m/r 5mg (n=59) vs. amlodipine 5mg (n=59) for 6 weeks. (Doses increased to 10mg if DBP ≥90mmHg after 2 weeks). | The differences in anti-hypertensive effect between treatments were marginal and not statistically or clinically significant at weeks 2 and 6. Both agents were well tolerated. The pulse rate did not differ between treatments either. No power calculation was carried out.  |

**Stable angina**

Calcium channel blockers (CCB) are generally as effective as beta-blockers in reducing symptoms of stable angina. (20;21) Beta blockers or CCB’s are recommended as first line treatments to reduce the symptoms of stable angina, depending on the patient's co-morbidities, contraindications and preference. (21;22) A rate-limiting CCB (such as diltiazem or verapamil) is preferred to a dihydropyridine CCB for stable angina. This is because:

* Rate-limiting CCBs have the additional action of decreasing myocardial contractility and heart rate.
* Dihydropyridine CCBs can sometimes cause reflex tachycardia, which may increase angina symptoms although this is more likely to be a problem with short-acting dihydropyridines than with longer-acting preparations. (21)

In patients who have heart failure or a history of heart failure, rate-limiting CCBs are contra-indicated and unless they have uncontrolled heart failure, these patients should be prescribed amlodipine or felodipine. (21)

In patients who require combination therapy, if they are taking a beta-blocker, a dihydropyridine CCB (such as amlodipine, felodipine, or modified-release nifedipine) is recommended. (21)

**Summary of clinical studies**

A few clinical studies (summarised in table 2) have compared the use of once daily amlodipine 5-10mg and once daily felodipine m/r 5-10mg in the treatment of stable angina.

Amlodipine appears to be as effective as felodipine m/r for stable angina based on clinical symptoms, exercise tests and 24 hour electrocardiogram (ECG) monitoring however definitive conclusions cannot be drawn from these few small studies.

**Table 2: Summary of clinical trials comparing amlodipine and felodipine m/r for stable angina**

|  |  |  |
| --- | --- | --- |
| **Diagnosis** | **Study Design** | **Basic Results**  |
| Exercise induced angina pectoris and myocardial ischaemia. 47 patients aged between 30 and 80 years. (23) | Prospective, randomised, double blind, double dummy, crossover study preceded by a 9 day run in period with placebo and long acting nitrates. The primary efficacy parameter was the number of ST-segment depressions during 24 hour ECG monitoring.Treatment: Felodipine m/r 5mg od vs. amlodipine 5mg od over 8 weeks with cross over at week 4. Doses were increased to 10mg after one week of each therapy.  | Both agents appear to be equally effective in reducing the number and duration of ischaemic episodes as well as the mean maximal ST-segment depression compared with baseline. No differences in tolerability were noted between the two treatments. |
| Stable exertional angina. 30 patients aged over 18 years. (24) | Randomised double blind, double dummy, parallel group study preceded by a 7 day wash out period with placebo and rescue GTN allowed throughout.The aim of the study was to compare the anti-anginal and anti-ischaemic effects of amlodipine and felodipine 4 hours after the first dose (acute effect) and 23 hours after the last dose (chronic effect). Treatment: Felodipine m/r 10mg (n=15) vs. amlodipine 10mg (n=15) for 4 weeks. | Both drugs reduced frequency of angina attacks and were well tolerated.Acute effects showed that felodipine m/r had a quicker onset of action than amlodipine. Chronic effects showed that felodipine m/r had greater improvements in exercise tolerance than amlodipine. |
| Mixed or exertional angina pectoris22 patients aged from 44 to 73 years. (25) | Multicentre, double blind, double dummy, crossover study preceded by a 7-day washout with placebo and rescue GTN.The aim was to compare the safety and efficacy of felodipine m/r with amlodipine. Treatment: Felodipine m/r 10mg vs. amlodipine 10mg od for 8 weeks with cross over at week 4. | The time to exercise test termination showed an increase with both drugs, which attained statistical significance only with felodipine m/r (p < 0.05). The duration of ischaemia showed a greater decrease that was more evident with felodipine m/r than with amlodipine without attaining statistical significance in either case. The decrease in the duration of angina pain also attained statistical significance with felodipine m/r but not with amlodipine. Adverse reactions considered as treatment related occurred in 8.3% of felodipine m/r cases and 25% of amlodipine cases. No power calculation carried out.  |

**Safety, tolerability and drug interactions**

Contraindications are comparable between felodipine m/r and amlodipine: some are unstable angina, cardiogenic shock, clinically significant aortic stenosis, and hypersensitivity to dihydropyridine calcium channel blockers. Both amlodipine and felodipine should be used cautiously in patients with impaired liver function. Grapefruit juice can increase the plasma levels of both amlodipine and felodipine so concurrent intake should be avoided with either drug. (1;2)

Substances that affect the cytochrome P450 3A4 enzyme system may affect plasma concentrations of amlodipine and felodipine. Enzyme inhibitors of CYP3A4 such as erythromycin and cimetidine may give rise to increased exposure to amlodipine or felodipine. Conversely concomitant use of CYP3A4 inducers such as rifampicin, carbamazepine and phenytoin may result in a lower plasma concentration of amlodipine or felodipine. Clinical monitoring and dose adjustment may thus be required. (1;2)

A [safety alert](https://www.gov.uk/drug-safety-update/simvastatin-dose-limitations-with-concomitant-amlodipine-or-diltiazem) was issued by the MHRA in 2012 regarding a drug interaction between amlodipine and simvastatin. The alert was based on the results of studies which showed that co-administration of simvastatin and amlodipine resulted in significantly increased exposure to simvastatin. Therefore, there is an increased risk of myopathy including rhabdomyolysis. Based on the available evidence, the MHRA recommend that the maximum daily dose of simvastatin should not exceed 20 mg when co-administered with amlodipine at doses of both 10 mg and 5 mg. (26)

There are currently no restrictions for co-administration of the other marketed statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin) with amlodipine. (1)

There is also currently no evidence to suggest that felodipine interacts with any of the statins. (2;3;27)

Additional information on interactions can be found in the Summary of Product Characteristics <https://www.medicines.org.uk/emc/> for both products.

**Switching from amlodipine to felodipine m/r and vice versa**

Four retrospective observational studies have reported on switching from amlodipine to felodipine in mainly hypertensive patients on a milligram-to-milligram basis. (28-31) One study found after switching from amlodipine to felodipine, the mean dose of felodipine was higher than that of amlodipine, 8.8 ± 3 and 8 ± 3 mg, respectively (p=0.02), therefore, the dosage homogeny anticipated between the calcium channel blockers was not observed. (28) Three studies reported on successful switch from amlodipine to felodipine on a milligram-to-milligram basis (29;30;31); two of these found no significant difference in blood pressure on follow up and one study showed a significant reduction in diastolic blood pressure 74 ± 9.5 to 72.6 ± 10.1 mmHg (p=0.032) however it also included other calcium channel blockers (29). It is difficult to compare the studies as the study designs and patient co-morbidities varied. Switching patients from amlodipine to felodipine at the same milligram dose may result in a need for dose adjustments or changes to the patient’s hypertensives. (29)

No data were found on switching from felodipine to amlodipine.

In all cases, monitor for adverse effects and response to treatment.

Limitations

* This review is limited to the comparison of amlodipine or felodipine. It does not compare the efficacy or safety of other dihydropyridine calcium channel blockers (e.g. lercanidipine) for management of hypertension or angina.
* This review does not include cost effectiveness data.
* The population size and quality of the studies involving head to head comparisons of amlodipine and felodipine m/r differ widely such that it is not possible to develop any meta-analysis given the variations in BP assessment, patient randomisation, blinding, etc.
* Statistical comparisons presented in this document are taken from published papers and in some cases, may be limited in their validity due to the small numbers of patients in some studies.
* There are only a few trials, incorporating small numbers of patients, comparing amlodipine and felodipine m/r in angina. Therefore, only limited conclusions can be drawn when comparing these two agents for this condition.

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### Search strategy

Please specify which of these are used if appropriate, (whether or not all of them yielded useful information) and add others if necessary:

1. Embase: FELODIPINE/cm (cm= drug comparison) AND AMLODIPINE/cm OR "AMLODIPINE BESYLATE"/cm OR "AMLODIPINE MALEATE"/cm AND exp HYPERTENSION/ OR exp "ANGINA PECTORIS"/[DT 2018-2020]. AMLODIPINE/ OR AMLODIPINE BESYLATE/ OR AMLODIPINE MALEATE/ AND FELODIPINE/ AND DRUG SUBSTITUTION/ OR DRUG COMPARISON/[DT 2018-2020].
2. Medline: [AMLODIPINE/ AND FELODIPINE/] AND [ANGINA PECTORIS/ OR HYPERTENSION/]/[DT 2018-2020]. AMLODIPINE/ AND FELODIPINE/ AND DRUG SUBSTITUTION/ OR THERAPEUTIC EQUIVALENCY/[DT 2018-2020].
3. Micromedex (amlodipine/felodipine comparison)
4. Cochrane library (amlodipine; felodipine)
5. NHS Evidence (amlodipine AND felodipine AND angina; amlodipine AND felodipine AND hypertension)
6. In-house resources (BNF, Martindale, Drugdex via [www.micromedexsolutions.com](http://www.micromedexsolutions.com), Stockley’s Drug Interactions)
7. SPC’s- Plendil, Istin