Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Calcium Channel Blockers

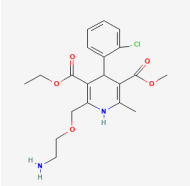
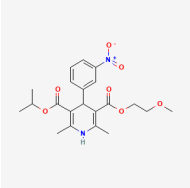
Evidence Summary

Calcium channel blockers reduce blood pressure and the risks associated with chronic hypertension. They also cause peripheral edema, dizziness, and potentially increase the risk of cancer.

Neuroprotective Benefit: Calcium channel blockers reduce blood pressure, which has corresponding vascular and neurological benefits. Some observational studies and small clinical trials have indicated potential benefit in prevention or treatment of dementia.

Aging and related health concerns: Calcium channel blockers effectively reduce blood pressure, as well as cardiovascular and cerebral vascular events.

Safety: Calcium channel blockers can cause peripheral edema, headache, and dizziness, among other common side effects. Some studies find an increased risk of cancer or certain cardiovascular events compared to other anti-hypertensives.

Availability: Rx	**Dose**: Amlodipine: 5-10 mg daily, orally (dose for hypertension) Nimodipine: 60 mg 4x/daily, orally (dose for subarachnoid hemorrhage)	**Chemical formula and MW**: Amlodipine $C_{20}H_{25}ClN_2O_5$  **MW**: 408.9 Source: PubChem Nimodipine $C_{21}H_{26}N_2O_7$  **MW**: 418.4 Source: PubChem
Half-life: Amlodipine: 30 – 50 hours Nimodipine: 1.7 – 9 hours	**BBB**: Permeable except for verapamil, diltiazem, and amlodipine, which have low to no penetrance	
Clinical trials: The largest meta-analysis of randomized controlled trials included over 100,000 patients.	**Observational studies**: The largest meta-analysis of observational studies included over 2 million participants.	

What is it?

As reviewed by Zamponi and colleagues (Zamponi et al., 2015, Zamponi 2016), calcium channel blockers (CCBs), also called calcium channel antagonists, primarily target L-type calcium channels (LTCCs). Upon binding to these long-acting voltage gated channels, calcium channel blockers prevent the flow of calcium ions into the cell. In the smooth muscle in blood vessels, blocking these calcium channels allow the blood vessels to vasodilate, which mediates their blood pressure lowering effects. There are 4 isoforms of L-type calcium channels: Cav1.1, Cav1.2, Cav1.3, and Cav1.4. Cav1.2 channels are found in the heart, blood vessels, and brain and Cav1.3 channels are also found in the brain, particularly on substantia nigra neurons. CCBs typically exert their studied relevant effects through one of these two isoforms. As L-type calcium channels are voltage gated, their opening/closing behavior depends not only on any chemical modulators in the environment, but also on cell-specific characteristics. For instance, these calcium channels may open at different thresholds in cells in blood vessels as compared to neurons. Different tissues also may have different splice variants of the channels, leading to unique effects of the drugs in various body compartments.

L-type calcium channels are located on the postsynaptic cell membrane. There, LTCCs are thought to modulate gene transcription changes in response to electrical or synaptic activity, thus playing a role in synaptic plasticity and long-term potentiation (LTP). LTP is thought to be a major molecular mechanism of learning and memory. About 90% of the brain's L-type calcium channels are Cav1.2-type, and the remaining 10% are Cav1.3 channels.

There are two broad classes of calcium channel blockers: dihydropyridines (DHP CCBs), comprised in the US of amlodipine, clevidipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, and nisoldipine, and the nondihydropyridines (non-DHP CCBs), diltiazem and verapamil (Siddiqi et al., 2019). There are many generic CCBs and other formulations that are approved outside of the US. Dihydropyridines generally bind to calcium channels in blood vessels and are prescribed for hypertension and angina; nonhydropyridines target channels in the heart and blood vessels, and so are prescribed for cardiac rhythm abnormalities as well as hypertension. Non-DHP CCBs have very little to no blood-brain barrier penetrance.

While all CCBs broadly are prescribed for conditions related to blood pressure, some have other indications. Amlodipine is the most commonly used CCB overall for hypertension. Nimodipine is prescribed for short-term use for those with subarachnoid hemorrhage, whereas nifedipine is often prescribed for blood pressure control in pregnancy as well as to help delay or prevent preterm labor. Clevidipine is available by IV formulation only and is typically used only in hospital contexts. These different indications may arise from binding affinities between particular DHP CCBs and certain tissue calcium channels, from affinities for other calcium channels such as N-type calcium channels, half-life of the medication, or other chemical variations.

This report will focus on DHP CCBs and on their effect on L-type calcium channels as most research has focused on this class's interaction with this subset of calcium channels.

Neuroprotective Benefit: Calcium channel blockers reduce blood pressure, which has corresponding vascular and neurological benefits. Some observational studies and small clinical trials have indicated potential benefit in prevention or treatment of dementia.

Types of evidence:

- 2 Cochrane meta-analyses
- 5 meta-analyses
- 14 observational studies
- 7 randomized controlled trials
- 2 open label trials
- 2 further or re-analyses of RCTs
- Numerous reviews and laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Several observational studies as well as a few randomized controlled trials have found decreased risk of cognitive impairment or dementia in patients who take CCBs.

SYST-EUR was a randomized controlled double-blind study assessing the effects of nitrendipine or two second-line antihypertensives versus placebo on the incidence of dementia. The initial trial was ended early due to significant results in favor of the treatment; the treatment group had a 50% lower incidence of dementia as compared to placebo (11 dementia diagnoses in the treatment group vs 21 in the placebo group, p = 0.05, corresponding to 3.8 cases vs 7.7 cases per 1000 patient years). The study then entered an open label phase. A paper with follow up results was published in 2002. This follow up paper included data from 2902 patients with a median follow up of 3.9 years. When the authors adjusted for sex, age, education, and blood pressure on entry to the study, they found that nitrendipine use was associated with lower risk of dementia as compared to placebo (HR=0.38; 95% CI, 0.23-0.64; P<.001) (Forette et al., 1999, Forette et al., 2002). This study was criticized for patient drop out and subsequent missing data.

The Leiden-85 Plus Study is a population-based study of 85-year-olds living in the Leiden district of the Netherlands. The authors assessed the change in cognitive function over 5 years of 204 participants who took anti-hypertensives. After controlling for sex, education, and use of other anti-hypertension

medications, the authors found that participants who used CCBs had significantly decelerated annual cognitive decline during follow up (0.40 MMSE-points per year, p=0.001). No other class of anti-hypertensive was linked to a slower annual decline in cognitive function (Trompet et al., 2006).

An observational study published in 2006 enrolled hypertensive elderly patients with memory complaints who attended an outpatient clinic. Patients were classified into four categories based on their cognitive function at the visit: cognitively unimpaired, mild cognitive impairment, Alzheimer's disease, or vascular dementia. The authors found that patients on anti-hypertensives performed better on the MMSE than unmedicated patients (MMSE score 23.9 ± 5.6 in treated patients versus 22.7 ± 6.4 in untreated patients), and that patients taking anti-hypertensives were less likely to be classified into their Alzheimer's disease group (OR=0.58; 95% CI 0.42 - 0.8). In the patients taking anti-hypertensives, use of CCBs as compared to other anti-hypertensive medication was also associated with a lower chance of being placed in the Alzheimer's disease category (OR=0.67; 95% CI 0.45 - 0.99). This effect was independent of blood pressure level (Hanon et al., 2006).

A 2016 paper examined electronic medical records in Taiwan in order to assess the effect of CCB exposure on the risk of developing dementia. They looked at records from 2000-2010 from 82,107 patients with hypertension and identified 16,956 patients who had CCB exposure of 3 months or more (12,174) and a comparator group who had not been on a CCB and had not taken any other antihypertensive for more than 3 months. Using propensity scores for age, sex, baseline co-morbidities, and time since hypertension diagnosis, the authors created 4004 matched pairs of CCB use and no CCB use. Over the follow up period of approximately 4 years, the authors found that the incidence of dementia in the CCB use group was significantly lower than in the group that did not use CCBs (3.9 vs 6.9 per 1000 person-years, p<0.01), and the risk of receiving a dementia diagnosis was significantly lower in the group with CCB exposure (HR = 0.53; 95% CI 0.39–0.72, P < 0.01). In sub-analyses, the authors found that the lower dementia risk correlated with increased dosage and with increased duration of CCB use. While there was not an increased rate of hypertension-related events in the comparator group, the design cannot rule out any confounder effects that arise from using a comparator group that did not use anti-hypertensives as long as the treatment group. The study also did not separate out the different CCBs specifically prescribed (Wu and Wen, 2016).

A study from Israel utilized electronic medical records to Compare the incidence of dementia after long-term (30 months+) treatment with either CCBs or another anti-hypertensive. They identified 15,664 hypertensive patients between the ages of 40 and 75 with no diagnosis of dementia. When the authors

adjusted for age, blood pressure, treatment time, stroke, and diabetes, they found a significantly lower risk of Alzheimer's disease in those treated with amlodipine (HR=0.60; 95% CI 0.48 – 0.74) (Feldmen et al, 2016).

A 2022 paper utilized electronic health records to create matched cohorts of 44,731 patients prescribed either BBB-penetrant or non-penetrant CCBs to examine the effect of the medication on incidence of neuropsychiatric disease and neurodegenerative disease diagnosis. In patients taking BBB-penetrant CCBs with no prior neuropsychiatric diagnosis, the authors found a lower risk of dementia diagnosis (RR=0.82; 95% CI 0.72–0.93) (Colboune & Harrison, 2022).

A recent study published in January 2023 followed 2234 community-dwelling older adults to assess the association between blood pressure variability and dementia risk, and whether that risk was modified by usage of anti-hypertensives. The patients had annual visits for up to 27 years. The authors found that higher systolic blood pressure at the 3, 6, 9, and 12 years was associated with a higher risk of dementia, but that this association was decreased in participants taking CCBs. The authors did not find a modified risk with any other anti-hypertensive treatment (Mahinrad et al., 2023).

Parkinson's disease

Three meta-analyses in 2015 & 2016 of cohort and case-control studies examined the incidence of Parkinson's disease (PD) in CCB users as compared to those who did not have CCB exposure (Lang et al., 2015; Gudala et al., 2015; Mullapudi et al., 2016). The three meta-analyses included many of the same studies, and all found that PD incidence was significantly lower in patients who had taken CCBs.

The largest meta-analysis, that of Mullapudi and colleagues, included 2,832,991 patients. Some studies specifically examined CCBs, and some examined four classes of anti-hypertensives: beta blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and CCBs. The follow up period of the included studies ranged from 4-16 years. The authors found that there was no overall association between the use of any anti-hypertensive and PD (RR=0.95; 95% CI 0.84–1.05). However, when looked specifically at CCB use, they found that there was a significantly lower incidence of PD in patients who were treated with CCBs as compared to those who were not (RR=0.82; 95% CI 0.71–0.93). There was significant heterogeneity in the included studies, but the authors performed a sensitivity analysis excluding each study one at a time and found that the results were robust (Mullapudi et al, 2016).

One of the studies included in the meta-analysis completed by Mullapudi et al was a cohort analysis by Lee and colleagues completed using electronic medical records in Taiwan. One notable finding from this paper was their subanalysis on dose and specific CCB used. The authors found that higher cumulative doses of felodipine (aHR = 0.54; 95% 0.36–0.80) and amlodipine (aHR = 0.60; 95% 0.45–0.79) were both associated with significantly lower PD incidence (Lee et al., 2014). Some preclinical work indicates that felodipine concentrates in the brain and may be efficacious in decreasing aggregate burden in multiple neurodegenerative diseases. (See 'Mechanism of Action for Neuroprotection' section for further information and details).

Human research to suggest benefits to patients with dementia:

A Cochrane meta-analysis from 2002 examined the effects of nimodipine in dementia patients. The included studies comprised of 2492 patients with dementias. When the authors pooled all dementia subtypes together, they found that 90 mg/day of nimodipine for 12 weeks had a benefit compared with placebo on the Sandoz Clinical Assessment Geriatrics (SCAG) scale (weighted mean difference[WMD]=7.59, 95% CI -9.87 to -5.31, P<0.00001), on clinical global impression (WMD=0.87, 95% CI -1.07 to -0.67, P<0.00001) and cognitive function (SMD 0.61, 95% CI 0.42 to 0.81, P<0.00001). They did not find differences on scales assessing daily functioning. They found similar results when they separated Alzheimer's disease diagnoses from vascular dementia. The authors found methodological issues with several trials and so while they found benefit and evidence that nimodipine is tolerated well, they called for further, longer, more rigorous trials to further explore the potential benefits (López-Arrieta and Birks, 2002, updated in 2005 and 2008).

Pantoni and colleagues examined the effects of nimodipine compared to placebo in patients with subcortical vascular dementia. This trial was not included in the above Cochrane meta-analysis, as the authors found the data 'difficult to interpret', perhaps in part because of differences in the number of patients randomized (242) to the patients who could be included in the per protocol analysis (149). Still, the study may be of some use in the context of this report.

The authors randomized 242 patients, with 124 taking nimodipine and 118 taking placebo, and assessed their cognitive function through a variety of measures at baseline and after 52 weeks of treatment. When they examined the cognitive function of patients in their primary outcome, the SCAG scale 5-point variation, the authors found that the 23.6% of the placebo group had worsened, whereas 13.8% of the

nimodipine treated group had worsened, though this difference was not statistically significant. The authors did find a significant improvement in the nimodipine group on a measure of lexical production. In a post-hoc analysis, they also created a subgroup of patients who had 1, 2, 3, or 4 point differences on their MMSE scores. They found that patients who had at least 3 point losses on their MMSE scores were more likely to be in the placebo group than the nimodipine group (28.1% of nimodipine group compared to 50.5% of the placebo group; $\chi 2$ $P<0.01$). The authors also reported that while their patient dropout was a limitation, proportionally more of the patient attrition was in the placebo group (86.3% of the nimodipine group vs. 65.2% of the placebo group completed the study, $p=0.0001$), and that more than 50% of the attrition in the placebo group was due to medical events such a cardiac event or stroke that theoretically could be a reflection of protection in the nimodipine group. They also found that the risk of psychiatric event was significantly increased in the placebo group as compared to the nimodipine group, which they speculated could be due to underlying disease progression (RR=3.88; 95% CI 1.49 – 10.12) (Pantoni et al., 2005).

Parkinson's disease

In light of preclinical work showing efficacy of isradipine as a potential neuroprotective agent in Parkinson's disease, a clinical trial named Steady-PD was initiated to test this CCB in patients with early-stage PD. After a Phase 2 dosing study of 100 patients, the authors selected a 5 mg daily dose of isradipine and randomized 336 patients to either placebo treatment or isradipine daily. They then followed the patients for 3 years. The primary outcome measure was progression on the Unified Parkinson's Disease Rating Scale (UPDRS), and secondary outcomes included time to initiation of PD medication, time to onset of motor complications, and quality of life measures. Disappointingly, the authors found no differences between groups on any measure (Steady-PD III Investigators, 2020). Subsequent re-analysis of both Phase 2 data and pharmacokinetic studies of Phase 3 participants indicate that the negative Phase 3 results could potentially be due to dosing. The re-analysis of the Phase 2 data indicated that 10 mg of isradipine daily may slow progression as measured by the UPDRS scale (Surmeier et al., 2022). In the pharmacokinetic substudy of the Phase 3 trials, a modest correlation was found between slower clearance of isradipine and less severe PD symptoms as assessed by cumulative dose of levodopa, the common medication prescribed to manage the motor symptoms of PD ($p=0.035$) (Venuto et al., 2021).

The authors postulated that these discrepant results may be in part due to the formulation of the medication. The early phase trials used an extended release version of isradipine that was discontinued

before the Phase 3 trial, necessitating the use of an immediate release version in the Phase 3 study. Taken together, these data indicate that while 5 mg daily of isradipine is not sufficient to slow progression of Parkinson's disease, there is a possibility that the proper dose or formulation may have some benefit in Parkinson's disease patients. The authors also suggested that isradipine or other calcium channel blockers may be more useful in prevention than in treatment.

Other studies have examined CCB use and dementia incidence and either not found an association between CCB use and decreased dementia risk, or found an association between anti-hypertensive medication and decreased dementia risk but no benefit of CCBs over other antihypertensives. The former category includes the Baltimore Longitudinal Study of Aging that enrolled 1092 patients and followed them for up to 19 years and compared DHP CCB users to non-users (RR = 0.30, 95% CI = 0.07-1.25, P = 0.10) (Yaser et al., 2005). The latter category included an observational study in Japan that enrolled 4124 patients and found no difference in incidence of AD diagnosis in patients that took CCBs compared to other anti-hypertensives (Ohrui et al., 2004) and a meta-analysis of 31,090 participants in observational trials that found an overall decrease in risk of dementia in hypertensive patients with use of anti-hypertensives (HR=0.88; 95% CI 0.79 – 0.98; p=0.019) but no difference between drug classes (Ding et al., 2020). Ding and colleagues found no decrease in dementia incidence in normotensive patients, and also found that CCB use trended towards significant decrease in dementia risk compared to no anti-hypertensive drug use (RR 0.83; 95% CI 0.67 - 1.01), but only in the high blood pressure group.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Calcium channel blockers may provide neuroprotection through indirect and direct means. Hypertension is linked to decreased cognitive function, and lowering blood pressure can increase cerebral perfusion and decrease hypoxia. CCBs, as anti-hypertensives, could therefore indirectly provide neuroprotection. CCBs also directly affect calcium homeostasis by blockading calcium channels. While calcium signaling is necessary for neuronal function, influx of too much calcium can trigger damaging cellular cascades. CCBs could therefore help prevent calcium-mediated damage including Aβ oligomerization and mitochondrial oxidative stress.

Amlodipine and the non-hydropyridines are thought to be only weakly penetrant through the blood-brain barrier (BBB), if at all, whereas the other dihydropyridine CCBs are all BBB penetrant. This may allow some differentiation between indirect and direct mechanisms of action. Some studies have found a decreased risk of dementia in patients who have taken BBB-penetrant CCBs as compared to

amlodipine or the non-hydropyridines. Colbourne & Harrison examined electronic health records to create matched cohorts of 44,731 patients prescribed either BBB-penetrant or non-penetrant CCBs to examine the effect of the medication on incidence of neuropsychiatric disease and neurodegenerative disease diagnosis. They found that in patients taking BBB-penetrant CCBs with no prior neuropsychiatric diagnosis, there was a decreased risk of dementia diagnosis (RR=0.82; 95% CI 0.72–0.93) (Colboune & Harrison, 2022). A meta-analysis by Lee and colleagues from 2014 found a decreased risk of Parkinson's disease with use of BBB-penetrant CCBs as compared to use of non-BBB-penetrant CCBs (adjusted HR=0.69; 95% CI, 0.55–0.87) (Lee et al., 2014).

Laboratory studies have identified differences in BBB penetrant vs non-penetrant calcium channel blockers. One study demonstrated that amlodipine and nilvadipine both reduced the production of Aβ40 and Aβ42 in vitro, and that nilvadipine and nitrendipine reduced brain soluble amyloid-beta in animal models. The authors also found that plasma amyloid-beta levels increased with CCB treatment, and they hypothesized that this was through increasing clearance of amyloid from the brain into the blood. Animals treated with nilvadipine had decreased plaque burden and improved spatial memory as measured by the Morris water maze (Paris et al., 2011).

Some lab studies suggest that CCBs may be autophagy inducers and can decrease the aggregate-load of several proteins involved in neurodegeneration, including tau, alpha-synuclein, and huntingtin. The work by Siddiqi and colleagues also demonstrated that felodipine is present at higher concentrations in the brain as compared to plasma in mice and minipigs. It is not known whether this is the case with any CCB in humans, or what the clinical relevance may be. Siddiqi et al. also found that felodipine protected against neurodegeneration in zebrafish tau models and in a mouse model of Parkinson's disease, and mitigated motor deficits in models both of Huntington's disease and Parkinson's disease (Williams et al., 2009; Siddiqi et al., 2019).

There may be a particular mechanistic benefit of CCBs in the prevention of Parkinson's disease. Cav1.3 L-type calcium channels are present in the part of the brain that canonically degenerates in PD, and are strongly engaged for rhythmic activity of these neurons. The successive inflow of calcium may cause or exacerbate damage, such as by increasing mitochondrial stress. Modulating these channels and thus the flow of calcium may therefore either mitigate or prevent damage in this PD-relevant neuronal population. Isradipine has the highest affinity for Cav1.3 channels, and has been studied for its potential disease-modifying effects (See 'Human research to suggest benefits to patients with dementia'). In some

animal models of Parkinson's disease, isradipine was shown to be neuroprotective. (reviewed in Zamponi et al., 2015, Ilijic et al., 2011).

APOE4 interactions:

A 2018 paper discussed the outcomes of a trial of 511 patients with mild to moderate dementia treated with placebo or nilvadipine, a CCB available in the EU and Japan. Nilvadipine did not slow progression, as measured by progression on ADAS-Cog 12 and CDR-sb. In a sub-analysis, the authors found that APOE4 carriers had less decline than non-carriers when treated with nilvadipine. However, the authors did not test for significance in their subgroup analyses (Lawlor et al., 2018).

Some preclinical evidence indicates that APOE4 may disrupt calcium homeostasis and increase calcium influx compared to other APOE genotypes; thus, calcium channel blockers may have a theoretical therapeutic mechanism of action (Ramakrishna et al., 2021, Jiang et al., 2015). One case cohort study examined 274 patients in an aging study who were diagnosed with dementia over the course of the study, and created a regression model to compare progression to dementia in patients who had used anti-hypertensives compared to those who did not. They also collected information about APOE genotype. The regression model indicated that CCB use was protective in both APOE4 carriers and non-carriers, and that CCB use in APOE4 carriers restored their progression to dementia to the levels of non-carriers who did not use CCBs (Lovell et al, 2015).

These data are too sparse to draw any firm conclusion beyond a possibility of a useful effect in APOE4 carriers.

Aging and related health concerns: Calcium channel blockers effectively reduce blood pressure, as well as cardiovascular and cerebral vascular events.

Types of evidence:

- 3 Cochrane meta-analyses
- 1 professional association guideline
- 2 meta-analyses
- 2 randomized controlled trial
- Numerous reviews and laboratory studies

Cardiovascular health: BENEFIT; USED AS FIRST-LINE TREATMENT FOR HYPERTENSION AND ANGINA

As per the American College of Cardiologists and the American Heart Association, calcium channel blockers are one of the first-line treatment options for hypertension and angina (Welton et al., 2017).

A 2003 meta-analysis looked at the benefit of anti-hypertensives, including CCBs, on cardiovascular events and mortality in a total of 162,341 patients in randomized controlled trials, and compared outcomes to placebo and to other anti-hypertensives. Compared to placebo, they found that patients who took CCBs had lower risk of stroke (RR=0.62; 95% 0.47 – 0.82), lower risk of coronary heart disease (RR=0.78; 95% CI 0.62 – 0.99), and major cardiovascular events (RR=0.82; 95% CI 0.71 – 0.95). There was a trend towards lower cardiovascular deaths in the CCB group compared to placebo group (RR=0.78; 95% CI 0.61 – 1.00) (Turnbull et al., 2003).

A 2004 meta-analysis examined the results of trials that randomized patients to CCBs or to another anti-hypertensive medication and assessed whether CCBs were associated with differences in incidence of stroke. The authors found that in 103,793 patients enrolled in the studies that CCB use was associated with a significantly reduced rate of stroke (OR=0.90; 95% CI 0.84 – 0.96; p=0.002) (Angeli et al., 2004).

The ACTION study was a double-blinded randomized controlled trial that compared treatment with nifedipine to placebo in patients with symptomatic coronary disease. The authors found that compared to the placebo group, the nifedipine treatment group had significantly reduced rate of overt heart failure (RR=0.71; 95% CI 0.54 – 0.94), coronary angiography (RR=0.82; 95% 0.75– 0.90), and bypass surgery (RR=0.79; 95%C CI 0.68 – 0.92) (Poole-Wilson et al., 2004). In a subgroup analysis of the 3997 patients who were hypertensive at baseline, the study authors found that compared to placebo, the nifedipine group had reduced incidence of overt heart failure (38% reduction; 95% CI HR 0.43–0.90); any stroke or transient ischemic attack (28% reduction; 95% CI HR 0.57–0.91); debilitating stroke (33% reduction; 95% CI HR 0.47–0.96), and the need for coronary angiography (16% reduction; 95% CI HR 0.75–0.96) (Lubsen et al., 2005).

In an RCT that enrolled 242 patients with vascular dementia to compare the efficacy of nimodipine as compared to placebo on cognitive function, the authors found a significantly increased risk of cardiac event (RR=2.25; 95% CI 1.11 – 4.60) and cerebral vascular event (RR=2.48; 95% CI 1.23 – 4.98) in the placebo group as compared to the nimodipine treated group (Pantoni et al., 2005).

A 2018 Cochrane meta-analysis examined each first line anti-hypertensive drug for their effect on morbidity and mortality compared to placebo or no treatment. The authors included randomized controlled trials that lasted for at least a year, and the meta-analysis included 58,040 patients across drug classes. CCBs comprised 4,695 of those patients. They found that compared to placebo or no treatment, CCB use reduced stroke (RR=0.58; 95% CI 0.41 - 0.84) and total cardiovascular events (RR=0.71; 95% CI 0.57 - 0.87). This data was from a single clinical trial of CCBs, SYST-EUR (Wright et al., 2018).

Safety: Calcium channel blockers can cause peripheral edema, headache, and dizziness, among other common side effects. Some studies find an increased risk of cancer or certain cardiovascular events compared to other anti-hypertensives.

Types of evidence:

- 1 Cochrane meta-analysis
- 4 meta-analyses
- 5 randomized controlled trials

Common side effects are dizziness, peripheral edema, hypotension, headache, muscle weakness, and GI symptoms.

Peripheral edema is a common side effect of CCBs. A 2011 meta-analysis of 99,469 patients enrolled in randomized controlled trials involving CCBs compared to another anti-hypertensive or a placebo found that 10.7% of CCB-treated patients reported peripheral edema, compared with 3.2% of patients in the control group. The authors found that 2.1% of CCB treated patients withdrew due to peripheral edema as compared to 0.5% in the control group. The incidence of peripheral edema increased with duration and dose of the CCB (Makani et al., 2011). Other groups have also reported significantly more peripheral edema in groups treated with calcium channel blockers, including the ACTION study, a double-blinded randomized controlled trial that compared treatment with nifedipine to placebo in patients with symptomatic coronary disease (Lubsen et al., 2005).

Rotshild et al., 2022 performed a meta-analysis examining the relationship between usage of calcium channel blockers and prostate cancer. In 18 studies comprising 226,501 CCB users and 315,924 non-

users, the authors found an increased risk of prostate cancer (RR=1.05; 95% CI 1.01 - 1.10) (Rotshild et al., 2022). Another meta-analysis of randomized controlled trials comprising 260,447 patients found that in comparison to other anti-hypertensive medications, use of CCBs may slightly increase the risk of a cancer diagnosis (HR=1.06; 95% CI 1.01 – 1.11), though no similar risk was seen when comparing CCBs to placebo (Copland et al., 2021). Authors of both papers wrote that the risks did not outweigh the benefits to hypertensive populations, and that further trials were needed to clarify and/or confirm the risk.

In the study by Pantoni and colleagues that examined nimodipine compared to placebo in patients with subcortical dementia, patients in the placebo group were significantly more likely to experience an adverse event (RR=1.29; 95% CI 1.03–1.61), or a serious adverse event (RR=1.58; 95% CI 1.03–2.42) as compared to patients in the nimodipine group (Pantoni et al., 2005).

Steady-PD examined the effects of isradipine compared to placebo in 336 patients with early Parkinson's disease. The authors found no difference in incidence of adverse or serious adverse events between the two groups: 4.1% of the isradipine treated group discontinued participation in the study due to an adverse event, compared to 1.8% of the placebo group. Of the reported side effects that affected 5% or more of patients, two were more frequent in the isradipine group: peripheral edema (18.2% of treated vs. 5.4% placebo) and dizziness (24.7% treated vs. 15.7% placebo) (Steady-PD Investigators, 2020).

A 2022 Cochrane meta-analysis compared risk of major cardiovascular events with CCBs as compared to diuretics, beta-blockers, ACE inhibitors, and ARBs. They included only randomized controlled trials with at least 100 participants that ran for at least 2 years, which totaled 153,849 patients. They found no difference in all-cause mortality (Zhu et al., 2022).

Table abbreviations: CV = cardiovascular; CHF = congestive heart failure

Drug Comparison	Major CV Event	CHF Event	Stroke	CV Mortality	Myocardial Infarction
CCB vs Diuretic	CCB Increase (RR=1.05; 95% CI 1.00 -1.09, P = 0.03)	CCB Increase (RR=1.37, 95% CI 1.25 -1.51)	No difference	No difference	No difference

CCB vs beta-blockers	CCB Reduce (RR=0.84; 95% CI 0.77 - 0.92)	No difference	CCB Reduce (RR=0.77; 95% CI 0.67 - 0.88	CCB Reduce (RR=0.90; 95% CI 0.81 - 0.99	No difference
CCB vs ACE Inhibitors	No difference	CCB Increase (RR=1.16; 95% CI 1.06 - 1.28,	CCB Reduce (RR=0.90; 95% CI 0.81 - 0.99	No difference	No difference
CCB vs ARBs	No difference	CCB Increase (RR=1.20, 95% CI 1.06 - 1.36	No difference	No difference	CCB Reduce (RR=0.82; 95% CI 0.72 - 0.94

Drug interactions:

Calcium channel blockers are contraindicated for people with hypotension, cardiogenic shock, and significant liver impairment. Particular care should be taken in patients with significant coronary artery disease and/or congestive heart failure. Some of the major interactions of the drug class include simvastatin (Zocor), certain anti-fungals such as itraconazole, some anti-epileptic drugs like carbamazepine, immunosuppressants like those used for patients who have had organ transplants, rifampin, anti-virals like ritonavir, and sildenafil or other medications that can lower blood pressure.

Drug & Reference	Number of Major Interactions	Number of Moderate Interactions	Number of Minor Interactions
Amlodipine	20	403	33
Clevidipine	4	228	3
Felodipine	20	380	21
Isradipine	17	361	23
Nicardipine	17	363	16
Nifedipine	26	473	42
Nimodipine	39	406	7
Nisoldipine	19	347	20

Research underway:

There are more than 400 ongoing trials in the US and EU that involve CCBs. Many focus on hypertension or blood pressure. Many of these trials involve amlodipine for conditions like hypertension, obesity, diabetes, and stroke. Trials involving nicardipine primarily involved conditions like stroke, aneurysm, or were pregnancy related; trials looking at nimodipine focus more on stroke or brain bleeding, and studies involving nifedipine largely involve pre- or postpartum hypertension and/or prevention or treatment of preterm labor. Four dementia-related trials with CCBs identified in the US use amlodipine, and one in the EU involves nimodipine.

Two studies from UT Southwestern are examining the effects of lowering blood pressure through medications including amlodipine on amyloid and tau deposition in older adults (NCT03354143) and in adults at risk of memory decline or dementia (NCT05331144). Secondary outcomes for these studies include cognitive performance and different aspects of brain health as measured by MRI.

One study in Brazil is investigating the effects of placebo vs. a multi-drug pill including amlodipine vs. lifestyle modification on stroke and cognition (NCT05155137) in a large cohort, with a target enrollment of 12,268 participants.

The last study is a prospective trial examining the impact of certain nutraceuticals and/or medications, including amlodipine, on cognitive impairment in older adults (NCT0496284).

One study in Europe is looking at the effects of nimodipine and placebo or nimodipine and choline alphoscerate on cognitive performance in patients with subcortical vascular dementia and mild to moderate cognitive impairment. The group aims to enroll approximately 60 people (EudraCT: 2015-003188-13).

Search terms:
Pubmed, Google: amlodipine, felodipine, isradipine, nimodipine, calcium channel blockers
Dementia, Alzheimer's, neuroprotection, Parkinson's, APOE

Websites visited for calcium channel blockers:

- ClinicalTrials.Gov: Calcium Channel Blockers; Amlodipine; Clevidipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nimodipine (No nisoldipine trials)
- Drugs.com: Calcium Channel Blockers; Amlodipine; Clevidipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nimodipine; Nisoldipine
- WebMD.com: Amlodipine; Clevidipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nimodipine; Nisoldipine
- PubChem: Amlodipine; Clevidipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nimodipine; Nisoldipine
- Drugbank.ca: Amlodipine; Clevidipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nimodipine; Nisoldipine