The latest 3rd Generation Calcium Channel Blocker

Dr Sameh Emil  M.D., FSCAI  Prof of Cardiology MMA

Prevalence of Hypertension
According to WHO reports:

1 in 3 adults suffer from hypertension
1 in 3 adults with hypertension do not know they have this disease
1 in 3 adults treating their hypertension cannot keep it under 140/90
Evolution of DHP Ca++ Channel Blockers

- **Long Receptor Half Life**
  - e.g. Lercanidipine

- **Long Plasma Half Life**
  - e.g. Amlodipine

- **Modified Release Formulations**
  - e.g. Nifedipine GITS, Felodipine XR

- **Rapid Acting**
  - e.g. Nifedipine

Abbreviations: GITS, gastrointestinal therapeutic system.
Antihypertensive actions, pharmacokinetics and side effects of three generations of DHP CCBs

The Latest 3rd Generation Ca++ Channel Blocker

- New long acting calcium channel blocker
  - **Lercanidipine Hydrochloride.**
  - For Management of Hypertension.

Short Plasma Half Life

Long Duration of Action
## Lercanidipine Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term treatment with lercanidipine in patients with mild to moderate hypertension</strong>&lt;sup&gt;30&lt;/sup&gt; 1997</td>
<td>Open, multi centre, n=355</td>
<td>Lercanidipine Diuretic, ACE or beta-blocker added if needed</td>
<td>After 4 weeks lercanidipine caused a significant decrease in BP (p&lt;0.001). Thirty-one (8.7%) patients complained of side effects, 4% of patients withdrew due to side effects.</td>
</tr>
<tr>
<td><strong>ELYSE</strong>&lt;sup&gt;26&lt;/sup&gt; 2002</td>
<td>Multi centre, open prospective observational study, n=9,059</td>
<td>Lercanidipine</td>
<td>Significant reductions in systolic and diastolic BP were observed after one month (p&lt;0.001). 6.5% of patients had an adverse reaction. Most commonly headache (2.3%), oedema (1.2%), flushing (1.1%) and palpitations (0.6%).</td>
</tr>
<tr>
<td><strong>LEAD</strong>&lt;sup&gt;23&lt;/sup&gt; 2003</td>
<td>Multi centre, double-blind, parallel group, n=250</td>
<td>Lercanidipine vs. felodipine GITS</td>
<td>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&lt;0.05). There was no significant difference in ADRs between lercanidipine and nifedipine GITS.</td>
</tr>
</tbody>
</table>

## Lercanidipine Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ELLE</strong>&lt;sup&gt;30&lt;/sup&gt; 2003</td>
<td>Multi centre, randomised, parallel group comparison trial, n=324</td>
<td>Lercanidipine vs. lacidipine* vs. nifedipine GITS</td>
<td>Systolic and diastolic BP was significantly decreased in all three study groups compared to baseline (p&lt;0.01). Incidence of ADRs was lowest in the lercanidipine group (19.4%).</td>
</tr>
<tr>
<td><strong>Tolerability of long-term treatment with lercanidipine versus amlopdine and lacidipine in elderly hypertensives</strong>&lt;sup&gt;34&lt;/sup&gt; 2002</td>
<td>Multi centre, double-blind, parallel study, n=828</td>
<td>Lercanidipine vs. amlopidine vs. lacidipine*</td>
<td>BP was significantly and equally decreased in all treatment groups (p&lt;0.01). Incidence of oedema was significantly higher in the amlopdine group 19% (p&lt;0.001) compared to lercanidipine (9.3%) and lacidipine* (4.3%) groups.</td>
</tr>
<tr>
<td><strong>Effects of lercanidipine vs. amlopdine in hypertensive patients with cerebral ischemic stroke</strong>&lt;sup&gt;36&lt;/sup&gt; 2015</td>
<td>Open label, controlled, randomised, parallel-group study, n=104</td>
<td>Lercanidipine vs. amlopdine</td>
<td>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 amlopdine group (5.7% compared to 19.2%).</td>
</tr>
</tbody>
</table>
Lercanidipine Trials

<table>
<thead>
<tr>
<th>Lercanidipine vs. felodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi centre, RCT, open-label, parallel group, n=281.</td>
</tr>
<tr>
<td>There was a significant decrease in BP compared to baseline for lercanidipine and felodipine ($p&lt;0.0001$). There was no significant difference between groups for BP lowering. AORs were 26.6% in the lercanidipine group and 25.3% in the felodipine group.</td>
</tr>
</tbody>
</table>

Lercanidipine in the management of hypertension: An update

Guido Grassi¹, Nicolás R Robles², Gino Seravalle³, Francesco Fici¹

Lercanidipine and HBP

Favorable Pharmacological Profile

-

-
Pharmacological Profile of Lercanidipine

- Elevated lipophilicity (15 times vs. amlodipine)
- High affinity for vascular membrane
  - Short plasma half-life \(\Rightarrow\) Prolonged tissue half-life
- High selectivity for vascular tissue
  - Lack of negative inotropic effect
  - Increased vascular protection
- Pharmacokinetic properties not affected by age
- Double route of excretion (renal and hepatic)
- No major drug-to-drug interaction

Lercanidipine Power of Innovation

- Afferent & Efferent Arteriolar Dilatation
  - Nephro-protective Effect
- Pre & Post Capillary Dilatation
  - Low Incidence of Ankle Edema
  - Lower central aortic pressure
In conclusion, treatment with lercanidipine at high doses is associated with a lower rate of adverse events related to vasodilation compared to high doses of amlodipine or nifedipine GITS in clinical practice.
DHP-CCB’s in HBP: lercanidipine

Favorable Pharmacological Profile

Effective Blood Pressure Control

BP and HR in response to different doses of Lercanidipine in patients with mild-to-moderate HBP

Circo A. J Cardiovasc Pharmacol, 1997
% of hypertensive patients normalized or responders to 4-week monotherapy with different doses of Lercanidipine

% patients

Normalized (BP <140/90 mmHg) Responders (BP decrease > 10%)

Circo A, J Cardiovasc Pharmacol, 1997

Antihypertensive efficacy of Lercanidipine (10-20 mg/day) in elderly HBP patients. The AGATE study

Office BP Home BP

Blood pressure (mmHg)

P<0.05

P<0.05

P<0.05

P<0.05

P<0.05

P<0.05

P<0.05

P<0.05

> 65 years < 65 years

Ribstein J et al, J Hypertens 2002
**Effects of Lercanidipine in elderly patients with ISH**

![Graph showing blood pressure changes with Lercanidipine and Placebo over 8 weeks of treatment.](image)

Despite similar reductions in peripheral systolic and PPs with the 4 classes of drug, changes in central pressure and augmentation index varied. Because central PP and increased wave reflections are considered important risk factors in patients with isolated systolic hypertension, the choice of therapy may be influenced by these findings in the future.
A randomized comparison between lercanidipine and amlodipine for efficacy and tolerability in patients with essential hypertension

Girish Tulshidas Rapartia, Balwant Kisanrao Choure3, Praveenkumar Tukaram Patilb, Shailesh Shyamling Patne4

<table>
<thead>
<tr>
<th>Duration</th>
<th>Systolic BP reduction (mean ±SD)</th>
<th>Diastolic BP reduction (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lercanidipine n=45</td>
<td>Amlodipine n=44</td>
</tr>
<tr>
<td>2 weeks</td>
<td>12.00±3.27</td>
<td>10.95±3.54</td>
</tr>
<tr>
<td>4 weeks</td>
<td>16.4±3.45</td>
<td>15.79±3.55</td>
</tr>
<tr>
<td>8 weeks</td>
<td>20.77±4.27</td>
<td>19.95±4.81</td>
</tr>
<tr>
<td>12 weeks</td>
<td>23.6±4.14</td>
<td>22.81±4.12</td>
</tr>
</tbody>
</table>

Conclusions: With the comparable antihypertensive efficacy, lercanidipine is associated with considerably lower incidence of vasodilation related side effects than amlodipine, especially pedal edema. This favourable tolerability profile can potentially enhance treatment outcome by promoting better adherence to drug therapy.

Lercanidipine is an effective and well tolerated antihypertensive drug regardless the cardiovascular risk profile: the LAURA Study

V. Barrios,1 C. Escobar,1 A. Navarro,2 L. Barrios,1 J. Navarro-Cid,1 A. Calderón1
On behalf of the LAURA Investigators
1Department of Cardiology, Hospital Ramón y Cajal, Madrid, 2Medical Department, Rescatari Spain, Madrid, Spain
Mean ± SD decreases in systolic blood pressure (SBP) in the four risk groups for cardiovascular disease during the study period when compared with baseline.

SBP Mean ± SD

- All Patients: n=3175
- Low: n=237
- Medium: n=1396
- High: n=722
- Very High: n=820

Cardiovascular Diseases Risk Groups

Mean ± SD decreases in Diastolic blood pressure (DBP) in the four risk groups for cardiovascular disease during the study period when compared with baseline.
**Mean SD Decrease in BP (SBP/DBP) in Four Risk Groups During Study Period**

- **Low (n=237):**
  - SBP: -18.5
  - DBP: -13.8
- **Medium (n=1396):**
  - SBP: -23
  - DBP: -15.2
- **High (n=722):**
  - SBP: -24.4
  - DBP: -16.1
- **Very High (n=820):**
  - SBP: -27.4
  - DBP: -17.4

Lercanidipine was effective and well-tolerated in patients with mild-to-moderate hypertension in the daily practice. The effectiveness and safety of the drug were independent of the degree of cardiovascular risk.

---

**Long-term outcomes of lercanidipine versus other calcium channel blockers in newly diagnosed hypertension: a nationwide cohort study**

*Kai-Hung Cheng, Kai-Chun Cheng, Kai-Yuan Cheng, Yi-Hsin Yang, Chung-Wei Lee & Wen-Ter Lai*

**Patients and methods:** A total of 144,630 newly diagnosed hypertension (HTN) patients (age: 18-65 years) in 2005 from the Taiwan's National Health Insurance Research Database were enrolled in this observational study. A pure hypertension population was fetched by excluding all chronic diseases in the Charlson Comorbidities Index. Patients were stratified into the **lercanidipine group (n = 1303)** and the propensity-score-matched comparative group (nifedipine, amlodipine or felodipine, n = 15,301).

**Results:** Compared to other CCBs, lercanidipine didn't have a significant difference on the study endpoints. In individual head-to-head comparisons, lercanidipine was shown to be superior to nifedipine in incident stroke with an adjusted HR with 95% CI of 0.526 (0.347-0.797) (p = .0025). The key limitations were that personal variables, such as smoking habits, alcohol intake, body mass index and physical activity and blood pressure profiles were not available in the nationwide registry database.

**Conclusion:** In newly diagnosed patients with hypertension, lercanidipine was superior to nifedipine in the six-year period when the analyzed endpoint was stroke.
Effects on office and home blood pressure of the lercanidipine-enalapril combination in patients with Stage 2 hypertension: a European randomized, controlled clinical trial

Giuseppe Mancia, Antonio Coca, Irina Chazova, Xavier Girerd, Hermann Haller, Paolo Pauletto, Danuta Pupek-Musialik, Yevgeniya Svyshchenko, on behalf of the FElt investigators

Journal of Hypertension 2014, 32:1700–1707

Conclusion: In Stage 2 hypertension, a fixed-dose combination of L and E ensures a control of both office and out-of-office BP, with a favourable tolerability profile.

Journal of Hypertension 2014, 32:1700–1707
**DHP-CCB’s in HBP: Lercanidipine**

- Favorable Pharmacological Profile
- Effective Blood Pressure Control
- Extensive Prevention/Regression of TOD

**Conclusions:** Our results show that in hypertensive NIDDM patients + lercanidipine induces a regression of LVH greater than losartan, independent of reduction in systemic blood pressure. It suggests that in this type of patients the Angiotensin II antagonism is less important than the calcium channel blockade for reversing LVH.

**Lercanidipine and TOD in Hypertension**

**Efficacy of Lercanidipine vs Losartan on Left Ventricular Hypertrophy in Hypertensive Type 2 Diabetic Patients:** P1.191

Conclusions: Our results show that in hypertensive NIDDM patients + lercanidipine induces a regression of LVH greater than losartan, independent of reduction in systemic blood pressure. It suggests that in this type of patients the Angiotensin II antagonism is less important than the calcium channel blockade for reversing LVH.
Indeed, both lercanidipine and ramipril treatments resulted in a significant reduction in AER without a statistically significant difference between the two groups.

**Research design and methods:**

- This was a 1 year, prospective, multi-center, randomized, open-label.

- Lercandipine + Enalapril Vs. Amlodipine + Enalapril

**Main outcome measures:**

- Renal function (albuminuria, serum creatinine, creatinine clearance, estimated glomerular filtration rate and proteinuria); blood pressure.
Conclusions. Lercanidipine at 20 mg dose, associated to a RAAS blocker, showed a high antihypertensive and antiproteinuric effect. This antiproteinuric effect seems to be dose-dependent as compared with previous reports and proportionally higher than blood pressure reduction.
Renal protection with calcium antagonists: the role of lercanidipine

Michel Burnier

Results:

Results from preclinical and clinical studies suggest that amlodipine is overall less effective in terms of renal protection when compared with other antihypertensive tested agents. Its beneficial effect in retarding the progression of renal disease is achievable only when combined with a blocker of the renin-angiotensin system. Conversely lercanidipine seems to provide renal protection in a similar way to ACE inhibitors, probably thanks to its mechanism of action which acts directly on the afferent and efferent renal arterioles.

Conclusions:

Treatment of hypertension with CCBs should take into consideration the special effects of each single agent at different levels: lercanidipine for example may play a useful role in the management not only of hypertension but also in renal protection of hypertensive patients.
Lercanidipine in Type II Diabetic Patients With Mild to Moderate Arterial Hypertension

Giorgio L. Viviani

Systolic BP

Fasting blood glucose

Diastolic BP

HbA₁

Lercanidipine in Patients with Chronic Renal Failure: The ZAFRA Study

203 CRF patients on ACEi or ARBS and reaching goal

Creatinine >1.4 mg/dL OR Creatinine clearance <70 mL/min

Blood pressure

Creatinine clearance

Proteinuria

(\( p=0.019 \))

(\( p=0.015 \))

2009 Renal Failure, 27:1, 73-80
Conclusions: Lercanidipine showed a high antihypertensive effect in CRF patients. It has a good tolerability profile and showed an interesting effect on plasma lipids. An improvement in renal function, measured through creatine clearance, was detected.

DHP-CCB’s in HBP: lercanidipine

- Favorable Pharmacological Profile
- Effective Blood Pressure Control
- Extensive Prevention/Regression TOD
- Improvement of the Metabolic Profile
- Favorable Tolerability Profile
Proportion of patients with AE’s after 3 months of treatment with lercanidipine in a population of 9059 patients. The ELYPSE trial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>% AE’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>INSIGH</td>
<td>49.0%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>VALUE</td>
<td>39.2%</td>
</tr>
</tbody>
</table>

Barrios V et al, Blood Pressure 2002

Is it possible to reduce the incidence of peripheral oedema using new generations of CCBs? Borghi et al. have shown that the occurrence of peripheral oedema can be reduced by 50% in patients who developed oedema with amlodipine and were switched to lercanidipine.
Comparative Effect of Lercanidipine, Felodipine, and Nifedipine GITS on Blood Pressure and Heart Rate in Patients With Mild to Moderate Arterial Hypertension: The Lercanidipine in Adults (LEAD) Study

Romito R et al, Am J Hypertens, 2003

Blood pressure

DBP  SBP

Treatment discontinuation for AE’s

Leg edema

% of patients

Calcium Channel Blockers
(Dihydropyridine derivatives)

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>Amlodipine</th>
<th>Nifedipine</th>
<th>Felodipine</th>
<th>Nilvadipine</th>
<th>Lercanidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Flushing</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Headache</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Palpitations</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>GI Disturbance, altered bowel habit</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Constipation</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Malaise</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Somnolence</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

*common adverse-effect; **very common adverse-effect.*
Prescribing trends in Ireland

DHP-CCB’s play a primary role in the treatment of HBP by reducing elevated BP values and the rate of major CV events.

Lercanidipine is highly effective in reducing BP both in the general population and in subgroups of high risk patients (elderly, ISH, diabetic, etc.)

The treatment with Lercanidipine is associated with an extensive target organ and metabolic protection in addition and beyond BP control.

Conclusions
Conclusions

✓ Its peculiar tolerability profile vs. other compounds of the same class, is an additional key feature that increases the clinical effectiveness of antihypertensive treatment and might reduce the costs of HBP.

✓ All these features may largely justify a primary role for lercanidipine for the management of the global cardiovascular risk in a large proportion of patients with HBP.

Thank You
Calcium antagonist lercanidipine improves endothelium-dependent vasodilatation of the brachial artery in patients with proved coronary vasospasm

63 patients with coronarographically proved coronary vasospasm. Subjects were assigned to treatment with lercanidipine without changing current treatment for six months.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>24-week treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical limitation</td>
<td>23 ± 18</td>
<td>40 ± 19</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angina frequency</td>
<td>35 ± 28</td>
<td>53 ± 28</td>
<td>0.002</td>
</tr>
<tr>
<td>Quality of life</td>
<td>22 ± 17</td>
<td>39 ± 22</td>
<td>0.005</td>
</tr>
<tr>
<td>Summary score</td>
<td>44 ± 12</td>
<td>87 ± 20</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Conclusion: The present study has demonstrated that a six-month treatment with lercanidipine improves flow-mediated dilatation in the brachial artery in patients with coronary vasospasm. Improvement of endothelial function in the brachial artery under the treatment with lercanidipine is accompanied by the improvement of chest pain characteristics and stress-induced ischaemic changes.