During the last decade the use of the antihypertensive drug class known either as calcium channel blockers or calcium antagonists in the treatment of hypertension and cardiovascular disease has been questioned. Ten years ago, various retrospective case-control studies suggested an increased incidence of myocardial infarction in patients treated with short-acting dihydropyridines, compared with other forms of antihypertensive treatment [1-3]. These results were supported by other case-control studies apparently showing other harmful actions of calcium channel blockers, such as an increase in cancer [4,5] incidence and gastrointestinal bleeding [6], and have been maintained in posterior studies [7].

In contrast, the clinical guidelines on antihypertensive treatment of the World Health Organization-International Society of Hypertension [8] in 1999 and the European Society of Hypertension and the European Society of Cardiology [9] in 2003 both recommended calcium channel blockers as first-line antihypertensive drugs and emphasized their capacity to be used in combination with most of the other antihypertensive drug classes, including thiazide diuretics, to better achieve blood pressure goals.

During the last six years a large body of evidence from well controlled clinical trials has clearly demonstrated the beneficial effects of calcium channel blockers in the treatment of hypertension and cardiovascular disease, in comparison to other drugs. Even so, calcium antagonists have been recently condemned by the same authors [10]. The most important studies carried out in hypertensive patients are the Nordic Diltiazem Study (NORDIL) [11], the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) [12], the Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) [19]. A metaanalysis published in 2003 by the Blood Pressure Lowering Treatment Trialists Collaboration [20] included some of these studies and the outcome data of other minor trials in order to examine the cardiovascular protection provided by calcium channel blockers in comparison to what has been called "conventional treatment" mainly thiazide diuretics and/or betablockers, and found no major differences in outcome among antihypertensive drug classes. Two more recent meta-analyses [21,22] have suggested a better effect of calcium channel blockers on cerebrovascular protection.

**Calcium Channel Blockers in Hypertension**

The NORDIL [11] and INSIGHT [12] studies both reported 6 years ago. In the NORDIL study [11] diltiazem was compared to conventional antihypertensive therapy (diuretics and/or betablockers) in more than 10000 hypertensive patients older than 50. Although the diltiazem group reduced systolic blood pressure 3 mmHg less than conventional therapy, no differences were observed in the primary objective (a combination of stroke, myocardial infarction and cardiovascular death). The total number of strokes was significantly reduced in the diltiazem group (RR: 0.80; p=0.04) with respect to conventional therapy.

Simultaneously, the INSIGHT trial [12] compared long-acting nifedipine against a combination of two diuretics (hydrochlorothiazide and amiloride) in more than 6000 high risk hypertensives. The occurrence of the primary outcome, a combination of stroke, myocardial infarction, heart failure and cardiovascular death, did not differ significantly between nifedipine or diuretic treated patients (RR: 1.10; p= 0.35). However, there were substantial differences in tolerability. Whereas symptomatic
adverse events, especially peripheral oedema, headache and flushing were more frequently seen in nifedipine-treated patients, metabolic abnormalities, such as hypokalemia, hyponatraemia, hyperlipidemia, hyperglycemia and hyperuricemia were clearly greater in diuretic-treated patients.

Prespecified subgroup analyses of the INSIGHT trial in diabetics [23] or patients with isolated systolic hypertension [24] revealed no significant differences between treatments, with the exception of new-onset diabetes, which was more common in hypertensives treated with co-amilozide (5.6% vs. 4.3%; p=0.023).

Silent target organ damage was investigated at two different levels in the INSIGHT study. Firstly, 201 patients were assessed for progression in coronary calcification, using double-helix computerized tomography. Nifedipine clearly inhibited coronary calcium progression compared with co-amilozide (3.18% vs. 27%; p=0.002 during the first year and 40% vs. 76%; p=0.002 at the third year) [25]. Similarly, carotid intima-media thickness progression was assessed by carotid ultrasonography. Intima-media thickness progressed in co-amilozide, but not in nifedipine-treated patients [26].

These two substudies of the INSIGHT trial clearly suggest that the calcium channel blocker nifedipine impairs the progression of vascular atherosclerosis. Although this effect had no impact on the clinical outcome during the relatively short period of the study follow-up, it is plausible to suppose that the lack of progression in vascular atherosclerosis (both coronary and carotid) would be beneficial in long-term cardiovascular protection. The slow down progression of carotid atherosclerosis by calcium channel blockers has also been observed in studies with lacidipine and amlodipine, but not with verapamil, whose primary endpoint was atherosclerosis progression. The Verapamil in Hypertension and Atherosclerosis Study [27] randomized 489 hypertensive patients to verapamil or chlortalidone.

Conversely, the European Lacidipine Study on Atherosclerosis [28] compared lacidipine versus atenolol in carotid atherosclerosis progression in 2334 hypertensive patients. In contrast with atenolol, lacidipine halted the increase in carotid intima-media complex thickness in both intention-to-treat and per protocol analyses. In patients with carotid plaques, a greater number of patients with plaque regression were observed in the lacidipine group, whereas plaque progression was more common in atenolol-treated patients. There were small, non-significant reductions in cardiovascular events, particularly strokes, in the lacidipine group. Similarly, in another study comparing amlodipine vs. placebo, Pitt et al [29] found that amlodipine reduced carotid intima-media thickness in patients with coronary artery disease. In addition, amlodipine reduced the rate of unstable angina or the need for coronary revascularization. These effects were obviously accompanied by differences in blood pressure reduction between amlodipine and placebo.

The ALLHAT [13] study is the largest trial of antihypertensive therapy conducted until now and included more than 30000 hypertensive patients older than 55 with an additional cardiovascular risk factor. Patients received antihypertensive treatment based on chlorthalidone, amlodipine, lisinopril or doxazosin, although this latter group was halted prematurely [30]. At 6 years of follow-up, the primary outcome (fatal coronary heart disease or non fatal myocardial infarction occurred in 11.3% of amlodipine-treated patients, 11.4% of lisinopril-treated patients and 11.5 of chlorthalidone-treated patients (RR of amlodipine versus chlorthalidone: 0.98; 95%CI: 0.90-1.07; RR of lisinopril versus chlorthalidone).

Despite this lack of differences in the primary endpoint, the ALLHAT investigators argued that chlorthalidone was superior to amlodipine or lisinopril in the treatment of hypertension, due to a better outcome in at least one secondary endpoint [13]. This argument also influenced the posterior JNC VII guidelines [31] which chose thiazide diuretics as first class therapy for "most" hypertensives.

In this trial, the comparison between amlodipine and chlorthalidone, although not significant, showed amlodipine tended to decrease total mortality (from 11% decrease to 2% increase) and stroke (from 18% decrease to 6% increase), even though systolic blood pressure was maintained between 1 and 2 mmHg higher in the amlodipine group throughout the study. The only difference favouring chlorthalidone over amlodipine was the incidence of heart failure, which was between 25% and 52% more frequent in the amlodipine group. However, the ALLHAT study was not prospectively powered to look for heart failure as an endpoint and heart failure was not defined by traditional criteria. The oedema was not well defined, occurred more commonly in the first study year, and was probably influenced by shifting patients abruptly from rational drug regimens to the study drugs on day 1 [32].

Despite these methodological problems in the ALLHAT trial, the question of an increased risk for heart failure development with calcium channel blockers has been raised due to the results of other clinical trials. In fact, both the INSIGHT [12] and the VALUE [15] trials reported higher rates of heart failure in nifedipine and amlodipine treated patients in comparison to hydrochlorothiazide-amilorida or valsartan treated patients. In these trials, independent committees confirmed the diagnosis of heart failure, although the influence of pedal oedema as a side effect of long-acting dihydropyridines cannot be completely ruled out.
The CONVINCE trial [14] included a total of 16476 hypertensives with an additional cardiovascular risk factor treated with controlled-onset extended-release verapamil or conventional therapy (atenolol or hydrochlorothiazide). No differences in the primary objective (stroke, myocardial infarction or cardiovascular death) were seen between groups (hazard ratio of verapamil versus conventional treatment: 1.04; 95%CI: 0.88-1.18). However the trial was planned as a non-inferiority study, and the upper limit of the 95% CI (1.18) exceeded the prespecified boundary of 1.16, meaning the non-inferiority could not be demonstrated. The study had two important limitations. Firstly, because obesity was the most frequent associated cardiovascular risk factor (50% of patients), the overall risk of hypertensive patients included was probably less than expected. Secondly, the study was prematurely stopped due to administrative reasons before a sufficient number of events occurred (less than one third of the planned number). These two important flaws make it difficult to regard the CONVINCE trial as conclusive.

The VALUE trial [15] included 15245 high-risk hypertensive patients older than 50 who were randomised to valsartan or amlodipine. The primary outcome was cardiac morbidity and mortality. After a mean follow-up of 4.2 years, the trial failed to show the superiority of valsartan over amlodipine in the primary endpoint (hazard ratio 1.04; 95%CI: 0.94-1.15). In contrast, amlodipine was superior to valsartan in the prevention of myocardial infarction (19%; p=0.02) and stroke (15%; p=0.08). This beneficial effect of amlodipine was mostly due to a better and faster blood pressure reduction and control.

The most recent trial published in hypertension with calcium antagonists is the ASCOT trial [16]. A total of 19257 hypertensive patients aged 40-79 with at least three other cardiovascular risk factors received amlodipine (most with added perindopril) or atenolol (most with added thiazide). The primary outcome was cardiac morbidity and mortality. The ASCOT trial was halted prematurely by the data safety monitoring board on the grounds that excess total mortality was observed in one of the treatment groups. Thus, although no significant differences were observed in the primary objective (hazard ratio of amlodipine compared to atenolol: 0.90; 95%CI: 0.79-1.02), a significant reduction in various secondary endpoints, such as all-cause mortality (11%), cardiovascular mortality (24%), stroke (23%), and the combination of myocardial infarction, stroke and cardiovascular death (16%) favoured the amlodipine group. This beneficial effect was also accompanied by better and earlier blood pressure control in patients treated with amlodipine (Figure 1).
Two recent meta-analyses enhance the idea that calcium channel blockers are superior to other antihypertensive class drugs in preventing stroke. In a review of 13 comparative trials, Angeli et al [21] found a statistically significant 10% decrease in the rate of stroke in patients treated with calcium antagonists (Figure 2). When this group was separated into dihydropyridines or not, the stroke reduction remained statistically significant in the former. A meta-regression analysis of these trials revealed that stroke prevention was clearly independent of blood pressure differences. More recently, the same investigators confirmed these results by comparing calcium channel blockers with conventional treatment or with angiotensin converting enzyme inhibitors [22].

### Table 1: Main results from the ASCOT-BPLA

<table>
<thead>
<tr>
<th>Objective</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CHD or non-fatal MI (including silent MI)</td>
<td>0.90 (0.79-1.02)</td>
<td>0.1052</td>
</tr>
<tr>
<td><strong>Secondary objectives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total coronary events</td>
<td>0.97 (0.79-1.10)</td>
<td>0.5070</td>
</tr>
<tr>
<td>Total CV events and procedures</td>
<td>0.84 (0.78-0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.69 (0.61-0.78)</td>
<td>0.0247</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.76 (0.65-0.90)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.77 (0.66-0.89)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0.84 (0.66-1.05)</td>
<td>0.1257</td>
</tr>
<tr>
<td><strong>Tertiary objectives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent MI</td>
<td>1.27 (0.60-2.20)</td>
<td>0.3088</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.68 (0.51-0.92)</td>
<td>0.0115</td>
</tr>
<tr>
<td>Stable angina</td>
<td>0.98 (0.81-1.19)</td>
<td>0.8323</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>0.65 (0.52-0.81)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Severe dysrhythmias</td>
<td>1.07 (0.82-1.38)</td>
<td>0.6009</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>0.70 (0.63-0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New onset renal failure</td>
<td>0.85 (0.75-0.97)</td>
<td>0.0187</td>
</tr>
<tr>
<td><strong>Post hoc analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary objective + revascularization</td>
<td>0.86 (0.77-0.96)</td>
<td>0.0050</td>
</tr>
<tr>
<td>MI + Stroke + CV mortality</td>
<td>0.84 (0.76-0.92)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Figure 1:** Main results from the ASCOT-BPLA
The renal effects of calcium channel blockers in these large hypertension trials have also been examined recently. In the INSIGHT trial, de Leeuw et al [33] observed a better protection against renal failure in patients treated with nifedipine GITS compared with hydrochlorothiazide-amiloride. In addition, a recent review concluded that calcium antagonists are effective in helping to control blood pressure (one of the main determinants of reduced renal function) in patients with chronic kidney disease and do not interfere with the antiproteinuric effect of renin-angiotensin system inhibitors when used in combination with these drugs [34].

In summary, the cardiovascular protection provided by calcium antagonists in hypertensive patients is at least as effective as that obtained with other antihypertensive agents, including conventional treatment with diuretics or beta-blockers [11-14,16] or newer drugs such as angiotensin-receptor blockers [15]. In addition, calcium channel blockers can be combined with other antihypertensive drug classes, including diuretics [15], producing early and effective blood pressure control that is essential for the cardiovascular protection of high-risk patients [15,16]. As most of these patients will require a combination of at least two hypertensive drugs to promote adequate blood pressure control [10,31], calcium channel blockers represent one of the preferred drug classes for this combination. Finally, their association with renin-angiotensin system blocking agents, such as ACE inhibitors [16] and, probably, angiotensin-receptor blockers, may yield additional benefits in cardiovascular protection and reduce the development of new-onset type 2 diabetes [16], which also has important prognostic implications [35].

**Calcium Channel Blockers in Coronary Heart Disease**

The INVEST trial [17] is the first of the three recent trials of calcium antagonists in patients with coronary heart disease. A total of 22576 hypertensive patients with established coronary artery disease were randomized to verapamil (with trandolapril added as required) or atenolol (with hydrochlorothiazide added as required). The primary outcome (death, myocardial infarction or stroke) occurred in a similar proportion in both groups (RR: 0.98; 95%CI: 0.90-1.06). No differences were observed in any of the secondary endpoints.

Short-acting dihydropyridines were the primary objective of most of the criticisms reported in the mid-1990’s. However, at that time, these short-acting drugs were largely replaced by long-acting formulations. In 2004, two studies examined the effect of either nifedipine or amlodipine in patients with coronary artery disease. Firstly, the ACTION trial [18] randomly assigned 7665 patients with stable symptomatic coronary disease to nifedipine GITS 60 mg daily or placebo added to usual treatment. The primary endpoint was the combination of death, myocardial infarction, refractory angina, heart failure, stroke or peripheral revascularization. There were no differences in this primary endpoint between patients treated with nifedipine or placebo (HR: 0.97; 95%CI: 0.88-1.07). Individual event rates were similar (death, myocardial infarction, refractory angina, stroke, or peripheral revascularization) or clearly reduced in the nifedipine group: new onset heart failure (29%), need for coronary angiography (18%) or coronary bypass surgery (21%).

A posterior analysis of the subgroup of hypertensives included in the ACTION trial (52%) revealed that the primary combined endpoint was significantly reduced in this subset (13%) [36].
Secondly, the CAMELOT study [19] included 1991 patients with angiographically documented coronary disease (>20% stenosis) who were randomized to amlodipine, enalapril or placebo. The primary endpoint was a combination of fatal and non fatal cardiovascular events. In the CAMELOT trial amlodipine significantly reduced the rate of the primary endpoint with respect to placebo (HR: 0.69; 95%CI: 0.54-0.88). The rate reductions of enalapril against placebo (15%) or amlodipine against enalapril (19%) were not statistically significant.

The CAMELOT trial included a substudy in 274 patients with measurement of coronary atherosclerosis progression by intravascular ultrasound (IVUS). The percent atheroma volume increased by 3.1% in the placebo group (p=0.001 from baseline), 1.9% in the enalapril group (p=0.08 form baseline), and 1.3 in the amlodipine group (p=0.31 from baseline). These three trials, as occurred in hypertensive patients without established cardiovascular disease, confirm the safety of calcium channel blockers in the treatment of patients with ischemic heart disease. Moreover, the results of the CAMELOT trial are very instructive and clearly suggest a similar or even a better effect of amlodipine with respect to enalapril in coronary atherosclerosis progression in this group of patients.

In conclusion, we have reviewed recent evidence supporting the clear benefit of calcium channel blockers in preventing cardiovascular disease in patients at risk (hypertensives). Moreover, this class of drugs is clearly safe when used in patients with coronary artery disease and probably preventive in those who are also hypertensive. Taken as a whole, this evidence suggest that long-acting calcium antagonists must be considered as first-line therapy in the prevention and treatment of cardiovascular disease, thus supporting the recommendations of the ESH/ESC guidelines [9].

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