Symposium Report

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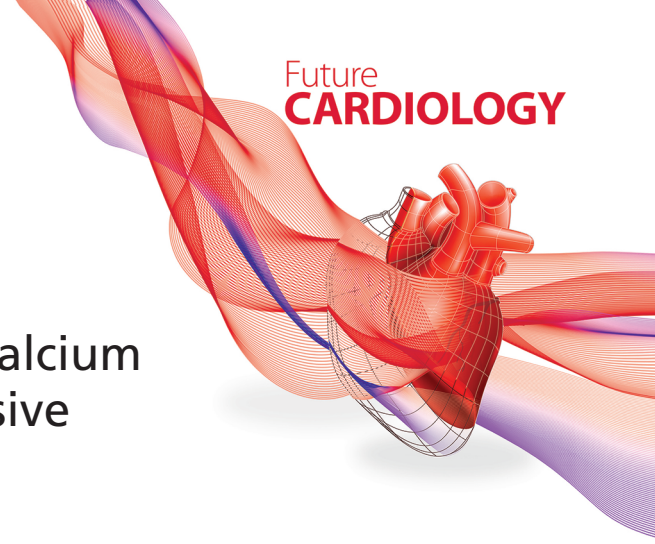

Current perspective on the use of calcium channel blockers to treat hypertensive patients: the role of lercanidipine

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The symposium '*Current perspective on the use of calcium channel blockers in the treatment of hypertensive patients*', held in Stresa (Italy) on 28th and 29th June 2018 with the participation of the main experts in the field of hypertension from all over the world, reviewed the role of calcium channel blockers in the management of hypertension. Considering the new European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines presented at the last European Society of Hypertension meeting in Barcelona in June 2018, a special attention was focused on lercanidipine. In this article, the main highlights of the symposium were summarized.

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Cardiovascular (CV) diseases are the world's biggest killer, and hypertension is the most important single contributor to CV morbidity and mortality. Despite advances in diagnosis and treatment over the past 30 years, the disability-adjusted life years attributable to hypertension have increased by 40% since 1990 [1]. Systolic blood pressure (SBP) ≥140 mmHg accounts for almost 70% of the mortality and disability burden, and ischemic heart disease (4.9 million), hemorrhagic stroke (2.0 million) and ischemic stroke (1.5 million) cause most of SBP-related deaths [1].

Combination of therapies to control hypertension & the role of calcium channel blocker

In new European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines, all five classes of antihypertensive agents currently available have proven ability to reduce blood pressure (BP) and constitute the basis of the antihypertensive therapy [1]. A meta-analysis described the linear relationship between the magnitude of BP reduction and the beneficial effect on hypertension-related outcomes; therefore, the BP reduction *per se* is the first advantage of an antihypertensive therapy, regardless the drug class used. Conversely, evidence of risk reduction of other CV events and, particularly, mortality are more specific to some drug classes only. For instance, Thomopoulos *et al.* in their meta-analysis of ten randomized clinical trials with a total of 30,359 patients showed significant reductions of stroke, major CV events, CV and all-cause death with calcium channel blockers (CCBs) [2,3].

Hypertension is associated or affected by numerous concomitant conditions, including old age, isolated systolic hypertension, diabetes, smoke, renal damage/failure, obesity and sleep apnea, left ventricular hypertrophy and organ damage, hypercholesterolemia, high CV risk, so it is often difficult to achieve BP control with monotherapy. A single drug can achieve the targeted SBP <140 mmHg in less than one patient out of four to five (almost 20–25%), and the result is worse even more with the lowered recommended target of BP (130/80 mmHg) [4]. Considering the limited results achievable with monotherapy, the new ESH/ESC guidelines [1] recommend a combination of two drugs to control hypertensive patients. For uncontrolled patients, the logical option is to increase treatment to three drugs, usually a renine-angiotensin system (RAS) blocker, a CCB and a diuretic [1]. The advantages of initiating treatment with two drugs, rather than monotherapy, are summarized in Box 1. The combination initially suggested is based on an RAS blocker and a CCB or a diuretic in uncomplicated hypertensive patients (Figure 1) [1].

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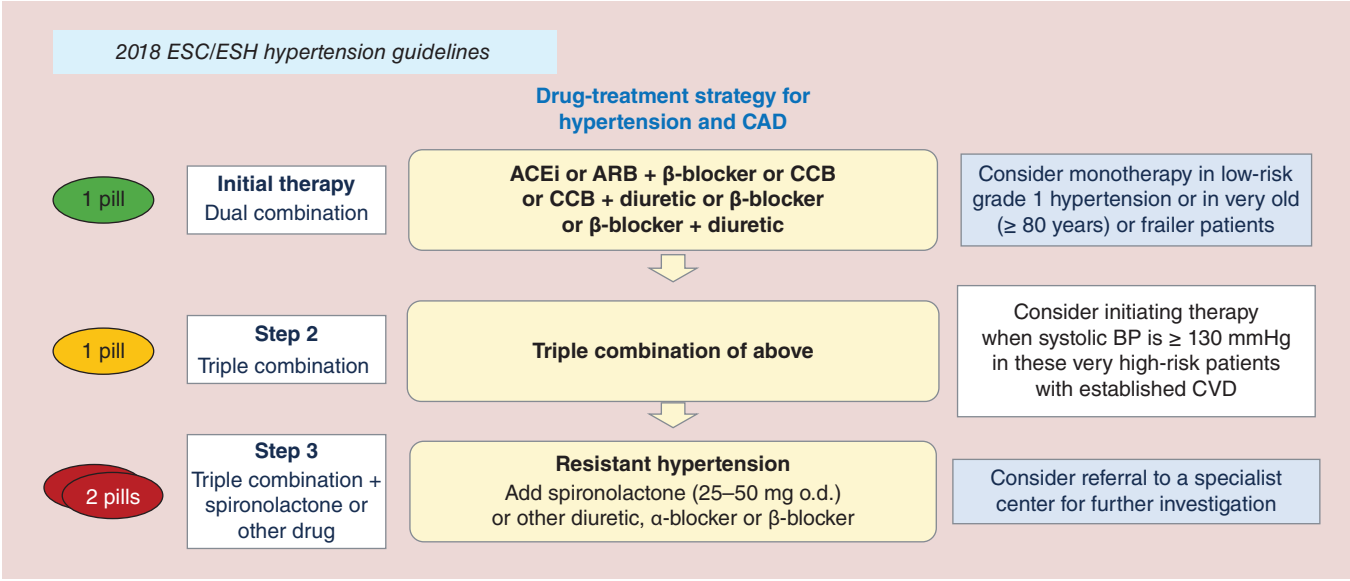

Figure 1. Polytherapy for blood pressure control in hypertensive patients, according to new European Society of Hypertension/European Society of Cardiology guidelines.
ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BP: Blood Pressure; CAD: Coronary artery disease; CCB: Calcium channel blocker; CVD: Cardiovascular disease.
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Box 1. Advantages of combination of therapy, as per new European Society of Hypertension/European Society of Cardiology guidelines.

1. Greater BP reduction even versus maximal dose monotherapy
2. Reduced heterogeneity of the BP response to initial therapy
3. Steeper dose–response relationship with treatment uptitration
4. No/minimal increase in risk of hypotensive episodes (even in grade 1 hypertension)
5. More frequent BP control after 1 year
6. Better adherence to treatment
7. Reduced therapeutic inertia
8. Reduced CV events (grade 1 hypertension, HOPE-3)

BP: Blood pressure; CV: Cardiovascular.
Data taken from [1].

New guidelines specifically recommended the presence of CCBs in the initial combination in presence of:

- Diabetes: RAS blocker + CCB or diuretics (recommendation of grade IA);
- Coronary artery disease: β-blocker (BB) or CCB + RAS blocker (IA);
- Chronic kidney disease (CKD): RAS blocker + CCB or diuretics (loop diuretics [D]);
- Cerebrovascular disease: RAS blocker + CCB or D (IA);
- Atrial fibrillation (AF): BB and/or nondihydropyridine CCB (IIaB);
- Hf(r/p*EF): RAS blocker + BB, diuretics + anti-aldosterone (IA) (*IIaB);
- Chronic obstructive pulmonary disease: RAS blocker + CCB;
- Lower extremity arterial disease: RAS blocker + CCB or diuretics (*BB may be considered);
- Blacks: D + CCB (IB).

The benefits in hypertension control of multitherapy overcome potential disadvantages. It should be, however, important to evaluate the characteristics of patients that may affect the adherence to treatment, and potential drug–drug interactions, especially when multiple morbidities are present. In addition, although CV risks associated with hypertension are well established and numerous effective drugs are available, the prevalence and adequacy of

these treatments are uncertain in persons with other CV morbidity [5]. In patients with coronary artery disease, congestive heart failure, stroke, chronic kidney disease, peripheral artery disease and diabetes mellitus, and distance to blood pressure goal, the rates of antihypertensive treatment are even higher than the rates of those without these conditions, but the control of systolic hypertension remains poor [5]. The correction of concomitant risk factors is pivotal to achieve the targeted BP and even to prevent the development of target organ damage (TOD) at the level of heart, kidney and vessels.

The most frequently TOD associated with hypertension is the left ventricular hypertrophy (LVH), which has deleterious consequences in terms of acute myocardial infarction, congestive heart failure, atrial fibrillation and sudden death [6,7]. Not all classes of antihypertensive drugs are equally effective in terms of LVH regression: angiotensin receptor blockers (ARBs), Angiotensin converting enzyme inhibitors (ACE-Is) and CCBs are the best therapeutic option to manage this condition [8].

Another frequent TOD associated with hypertension is the end-stage renal disease, whom incidence is directly correlated to hypertension severity [9]. A meta-analysis of randomized clinical trials did not find any difference in terms of benefits among antihypertensive agents [10]. However, new CCBs that induce vasodilation at the level of both afferent and efferent renal arteriole might have beneficial effects on kidney function in patients with hypertension [11].

As far as vessels are concerned, a different effect of antihypertensive drugs on small artery remodeling has been demonstrated: ACEIs, ARBs and CCBs induce greater regression of small artery remodeling and improve the endothelial function compared with diuretics and BBs [12]. The use of multitherapy with drugs, which present different mechanisms of action, may contribute to limit TOD, as well as to improve the burden of hypertension. The choice of antihypertensive drugs, however, cannot be based only on potential clinical benefits, but also the adverse events expected with each class of agents should be considered.

Indeed, the presence of adverse events affects the adherence to therapy and, in many cases, may cause discontinuation. The rate of treatment discontinuation for adverse events has been recently defined as a potential measure of treatment tolerability, frequently evaluated also in randomized controlled trials [13]. All classes of drugs significantly increased discontinuations for adverse events over those occurring on placebo, with the single exception of angiotensin receptor blockers [13]. CCBs have proven to be safe, despite the controversy in the past and the concerns related the acute effects of some CCBs, such as nifedipine, do not apply to new CCBs like lercanidipine, which are not associated with sympathetic activation.

Need for a personalized therapy to achieve BP goal

New guidelines highlight the importance to both achieve BP control and reduce the CV risk, keeping in account all other risk factors that may affect clinical outcomes and the potential adherence to treatment. CCBs are indicated as first-step agents in the treatment of hypertension, either as monotherapy or in combination with other classes. CCBs can be combined with almost every class of antihypertensive drug and this clinical flexibility allows their extensive use in everyday clinical practice. The choice of a CCB in the single patient should consider treatment schedule, patient profile, pharmacological differences between drugs and evidence beyond BP control. This may allow tailoring antihypertensive treatment for each individual patient, with a positive impact on adherence and clinical outcomes.

Focus on lercanidipine

Lercanidipine belongs to the third generation of CCBs, characterized by high vascular selectivity and persistence in the smooth muscle cell membranes. The first short-acting CCBs (e.g., nifedipine and felodipine) produced unwanted reflex tachycardia; these drugs were, therefore, modified to prolong the action and limit adverse effects (long plasma half-life) [14].

Cicero *et al.* showed the effect of lercanidipine in combination with other drugs on BP reduction and metabolism in 162 hypertensive patients [15]. Patients received a combination of lercanidipine (10–20 mg/day) with β-blockers, diuretics, angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers according to ESH/ESC guidelines. As expected, the combination decreased BP more than lercanidipine alone, regardless of the drug type added (p-value always <0.05). Furthermore, significant decrease in fasting plasma glucose and serum levels of triglycerides was achieved with the combination of lercanidipine and angiotensin-converting enzyme inhibitor or an angiotensin-II receptor blocker [15]. In the ELIPSE study, a subgroup of patients with diabetes mellitus 16.4% achieved an adequate BP ($<130/85$) control with lercanidipine; this result was lower than that obtained in overall

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population (32%), but it was significant if considered the low incidence of adverse events reported in the trial [16]. As reviewed by Grassi *et al*. lercanidipine displays a renal protection with a significant decrease of microalbuminuria and improvement of creatinine clearance in patients with diabetes and renal impairment [17].

Lercanidipine was well tolerated in uncontrolled and controlled studies; it produced no significant heart rate changes, while most adverse events were the result of vasodilatation early in the treatment [14]. A favorable safety profile is of pivotal importance in the choice of an antihypertensive therapy in which the presence of potential side effects cannot be considered as a negligible problem, especially in certain population. For example, in elderly patients, lercanidipine showed similar efficacy to amlodipine, but a better tolerability profile, with a lower rate of edema and early drug discontinuation due to edema [18]. Numerous studies have shown that treatment with lercanidipine is associated with a very low rate of adverse events and withdrawal from the therapy. Even if the rate of adverse events differs across studies, overall 11.5–11.8% of patients reported adverse events and a very low percentage (1–2%) discontinued lercanidipine treatment due to adverse events [17]. Since treatment discontinuation is an heterogeneous phenomenon within each class of antihypertensive drugs, the evaluation of the cost to benefit ratio of a treatment should be drug based, rather than class based [19–21].

The combination of lercanidipine + enalapril lowers hypertension more effectively than the corresponding monotherapies and placebo: this greater effect is consistent between days [22] and seems to be dose dependent with different combinations of dosing [22]. This combination has also a beneficial effect against TOD. Indeed, lercanidipine + enalapril showed more improvement than lercanidipine + hydrochlorothiazide in terms of reduction of retinal wall thickness [23].

The difference in the mechanism of action of lercanidipine versus other CCB provides some advantages in renal protection. Indeed, lercanidipine acts on both afferent and efferent renal arterioles, reducing BP inside the glomerulus and improving hyperfiltration [11]. Furthermore, while classic CCBs showed detrimental effects on microalbuminuria, for example, in the ACCOMPLISH trial where patients treated with hydrochlorothiazide in addition to benazepril were more likely to present decrease or remission of microalbuminuria compared with patients treated with amlodipine [24], lercanidipine had positive effects. In the DIAL study, ramipril and lercanidipine showed a similar effect in patients with hypertension and diabetes, in terms of both BP reduction and regression of albuminuria [25]. In the ZAFRA study, lercanidipine 10 mg added to the ongoing RAS blocker treatment in chronic renal failure patients with BP >130/85 mmHg resulted in an improvement in BP control, mild increase in creatinine clearance and reduction in lipids [26]. Interestingly, the study was repeated in patients with proteinuria treated with lercanidipine 20 mg: proteinuria was reduced faster and deeper than with lercanidipine 10 mg, thus suggesting a dose-dependent activity [27]. In the RED LEVEL study, patients with diabetes and/or chronic renal disease were treated with enalapril + lercanidipine or enalapril + amlodipine: both BP and albuminuria were equally reduced in both arms, but lercanidipine achieved a persistent improvement [28]. The availability on the market of two formulations of lercanidipine (10 and 20 mg) contributes to satisfy the therapeutic need of those patients who have severe hypertension and require a higher daily dose. The 20-mg formulation provides therapeutic convenience in a single once daily administration and it may favor a better compliance to treatment.

The reason for this differential activity of lercanidipine compared with traditional CCB is related to its ability to inhibit both L- and T-type calcium channels. In the afferent arterioles both L- and T-type calcium channels are present, whereas in the efferent arterioles only T-type channels are found [29]. A voltage clamp model was used to measure the calcium current mediated by L- and T-type calcium channels, in order to evaluate the selectivity of different CCBs [30]. All dihydropyridine CCBs were shown to block >50% of L-type channels. Lercanidipine had shown to block both L- and T-type channels, with the highest T/L selectivity: this could be translated into beneficial clinical effects by vasodilating both afferent and efferent glomerular vessels and exerting renal protection [30]. Thus, lercanidipine, by acting on both L- and T-type calcium channels, has a strong vasodilatory effect on both efferent and afferent glomerular arterioles, thus alleviating glomerular hypertension. Furthermore, both T-and L-type calcium channels regulate vascular smooth muscle tone, also on cardiomyocytes, where they contribute to cardiac pacemaking and conduction [31].

Overview of new ESH/ESC guidelines & their clinical implications

New guidelines highlight how it is important to carefully monitor hypertensive patients, as already done before. The screening should be done at least once in all adults and regularly repeated. When BP levels in the hypertensive range are detected, these values must be checked over time to confirm diagnosis, either with repeated visits to repeat office BP measurement or, when it is economically feasible, using out of office BP measurements.

Although BP classification and the definition of hypertension grade (optimal, normal, high-normal or grade 1-3 hypertension) according to office BP have been maintained, new guidelines emphasize the use of alternative methods for BP measurement, such as ambulatory blood pressure monitoring and home-based pressure measurement (HBPM). Ambulatory blood pressure monitoring and HBPM can identify white-coat and masked hypertension, have a stronger prognostic evidence and allow night-time readings. These measurements are performed in real-life setting and provide numerous information from a single session, including short-term BP variability; however, they may be more expensive and generate some discomfort for patients or can measure only static BP, as in the case of HBPM.

It is recommended that all hypertensive patients undergo pulse palpation at rest to determine heart rate and search for arrhythmias and atrial fibrillation; other BP measures and indices (pulse pressure, BP variability, exercise BP, central BP and unattended BP measurement) may be considered. In the view to treat hypertension and all potential risk factors for CV disease, a careful monitoring of laboratory test is recommended.

New guidelines include recommendations for diagnostic workup of patients with a suspected hypertension emergency (hypertensive crises or other medical conditions requiring a rapid reduction of BP levels through intravenous antihypertensive drug administration) and specific recommendations are given for the diagnosis of resistant hypertension and for the identification of causes of secondary hypertension. The assessment of hypertension-mediated organ damage is an important part of the diagnostic workout, while the 10-year CV risk should be assessed through the SCORE system categories (SCORE system), using correction factors for first-generation immigrants to Europe. The SCORE system is recommended to assess CV risk for hypertensive patients who are not already at high or very high risk due to established CV or renal disease or diabetes or a markedly elevated single risk factor (e.g., cholesterol), or hypertensive LVH. As in previous guidelines, the new version classifies hypertension stages according to BP levels, presence of CV risk factors, hypertension-mediated organ damage (HMOD), comorbidities.

Whatever type of treatment is adopted, the new guidelines expand the need of drug treatment to categories for which the benefits were not certain or treatment was not recommended by previous guidelines:

- Grade 1 hypertension in the elderly: in previous guidelines, treatment was recommended in the elderly only if they had grade 2 or 3 hypertension (peripheral arterial stiffness (PAS) $\geq$160 mmHg). In recent trials where entry BP was $\geq$140 mmHg, treatment was beneficial for elderly patients over 65 years;
- Grade 1 hypertension at low-to-moderate risk: according to recent data from the prespecified subgroup analysis of the HOPE 3 trial, if BP is reduced in patients with grade 1 hypertension at low–moderate risk, there is a beneficial effect: patients with initial PAS >143.5 mmHg (mean PAS 154 mmHg) showed a significant reduction of the incidence of CV events after treatment. Furthermore, in patients with grade 1 hypertension and low-to-moderate risk, BP reduction was associated with a significant reduction of CV events;
- High normal BP (some patients): in previous guidelines, treatment was not recommended in patients with high normal BP, based on the absence of data from randomized clinical trials. Therefore, among the very large category of patients with PAS values between 130 and 139 mmHg we must recognize those with high or very high CV risk, who can be candidates to drug treatment to reduce PAS <130 mmHg.

According to the BP thresholds for treatment reported by new guidelines, an SBP value $\geq$140 mmHg is recommended in virtually all patients, except in patients $\geq$80 years old, for whom the threshold remains the same as in previous guidelines.

Target BP values have been lowered to <140/90 mmHg in all patients and <130/80 mmHg or lower in most patients if tolerated. To achieve this goal, the recommended drugs include all the five classes of antihypertensive drugs currently available. The most effective evidence-based treatment strategy to improve BP proposed by new guidelines includes use of combination treatment, use of single-pill combinations (also as initiation therapy) and application of simple treatment algorithms. Follow-up is also important, after the initiation of antihypertensive drug therapy, it is crucial to review the patient at least once within the first 2 months to evaluate the effects on BP and assess possible side effects until BP is under control. SPC therapy should reduce BP within 1−2 weeks and may continue to reduce BP over the next 2 months; verify BP control at 3 and 6 months; assess risk factors and asymptomatic organ damage at least every 2 years.

Since hypertension control remains poor, it is important to improve patients' adherence: it is well accepted that lower adherence to therapy is associated with worse reported CV outcomes. A collaborative approach between nurse, pharmacist, physician and specialist is essential to maximize the adherence.

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The potential advantages of lercanidipine fit well with the recommendations of new ESC/ESH guidelines. Lercanidipine has an innovative mechanism of action and can be easily and safely used in combination with other antihypertensive drugs; it is available in two formulations to comply the therapeutic need of patients with severe hypertension; it shows a favorable tolerability profile, which can enhance the adherence to treatment. In order to achieve hypertension control in clinical practice, educational programs should be planned to disseminate current perspectives of guidelines and potential advantages of novel drugs, including lercanidipine, in primis among general practitioners who first managed hypertensive patients.

Conclusion

New ESH/ESC guidelines highlight the importance to control BP and concomitant conditions to overall reduce the CV risk. Among available therapeutic options, CCBs are pillars of antihypertensive therapy; their flexibility allows using them in a broad range of combinations in patients who presented specific medical needs. Lercanidipine is a third-generation CCB characterized by reduced adverse events in comparison to other CCBs. This molecule may be considered in patients at high risk of TOD and in elderly ones. Therefore, current management of hypertension should be tailored on each patient to maximize the clinical benefit and improve the adherence to treatment.

Future perspective

Future management of hypertension should be tailored toward each patient to maximize the clinical benefit and improve the adherence of treatment. A wide range of safe and efficient therapeutic options will be available and, therefore, difficult-to-manage patients can also achieve favorable clinical outcomes. In this view, an important role is played by lercanidipine, a third-generation CCB that is characterized by reduced adverse events in respect to other CCB. Safety and high tolerability will progressively be the determinants in the choice of therapeutic approaches, considering the frequency of comorbidities and the aging of patients.

Executive summary

- Hypertension can be considered as a public health epidemic.
- The choice of antihypertensive drugs is based not only on efficacy and potential clinical benefit but also on the expected burden of adverse events associated with each class of agents.
- New guidelines highlight the importance to both achieve blood pressure control and reduce the cardiovascular risk, keeping in account all other risk factors that may affect clinical outcomes and the potential adherence to treatment.
- Calcium channel blockers (CCBs) are pillars of antihypertensive therapy; their flexibility allows using them in a broad range of combinations in patients who presented specific medical needs.
- Lercanidipine is a third-generation CCB characterized by a reduced incidence of adverse events when compared with other CCBs.

Author contributions

G Mancia and K Tsioufis equally contributed to this work.

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