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“钙离子拮抗剂在高血压治疗中的应用前景：乐卡地平的作用”  
文献解读

医学及信息部—信息事务组

2019-07-12



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- 聚焦乐卡地平
- 专家共识意见
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传递最有价值的医学信息

01

# 文献简介

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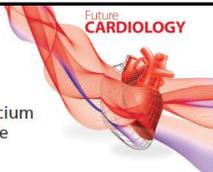


## Current perspective on the use of calcium channel blockers to treat hypertensive patients: the role of lercanidipine

### 钙离子拮抗剂在高血压治疗中的应用前景： 乐卡地平的作用

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Symposium Report  
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#### Future CARDIOLOGY

### 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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**Keywords:** calcium channel blocker • hypertension • lercanidipine

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)  $\geq 140$  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 (2). 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) (3,4).

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) (5). 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 renin-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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专题研讨会要点总结



## ——专题研讨会-基本信息

### 会议主题

钙离子拮抗剂在高血压治疗中的应用前景：乐卡地平的作用

### 会议时间

2018年6月28-29日

### 会议地点

意大利

### 参会人员

世界各国高血压领域专家



# 02

## 文献内容摘录解读

- 2018 ESC/ESH高血压指南解读
- 聚焦乐卡地平
- 专家共识意见
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# 2018 ESH/ESC高血压指南解读

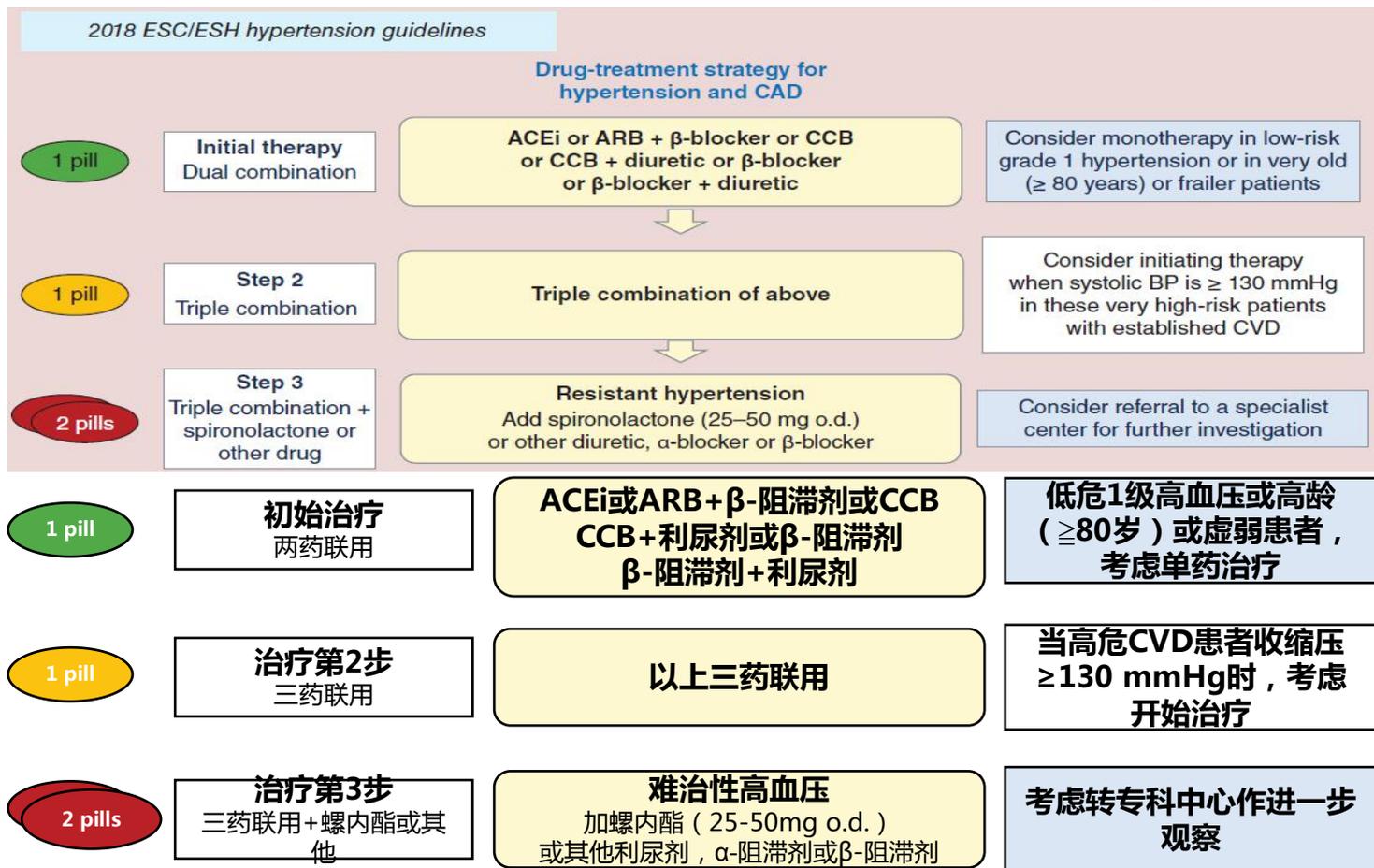
高血压是导致心血管疾病发病和死亡的最重要因素

考虑到单药治疗效果有限，新的欧洲高血压学会/欧洲心脏病学会（ESH/ESC）指南推荐两种药物联合使用来控制高血压患者

收缩压 $\geq 140$ mmHg在导致死亡和伤残负担的疾病中占约70%，其中缺血性心脏病(490万)、出血性脑卒中(200万)和缺血性脑卒中(150万)，是收缩期高血压相关死亡的主要原因

对于未受控制的患者，合理的选择是将治疗增加到三种药物，通常是肾素-血管紧张素系统(RAS)阻滞剂、钙离子拮抗剂（CCB）和利尿剂

### ➤ 2018 ESH/ESC高血压指南：高血压和冠状动脉疾病的药物治疗策略



### 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].

1. 与最大剂量单药治疗相比，具有更好的降压效果
2. 减少高血压初始治疗的异质性
3. 随着剂量加大，具有更陡峭的剂量-反应关系（斜率更大）
4. 无/最小的增加低血压发作风险(即使是1级高血压)
5. 1年后血压控制效果更好
6. 更好地坚持治疗
7. 治疗惯性减少
8. 心血管事件减少(1级高血压，HOPE-3)

1. Williams B, Mancia G, Spiering W et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology, ESH/ESC Task Force for the Management of Arterial Hypertension. J. Hypertens. 36(12), 2284–2309 (2018).



## ——钙离子拮抗剂的作用

### ➤ 指南特别推荐在联合用药中使用钙离子拮抗剂，当存在以下情况时：

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:  $\beta$ -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).

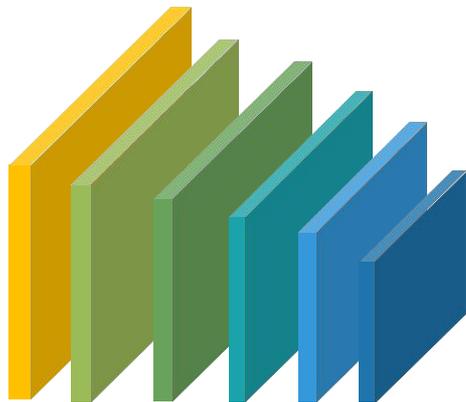
- 糖尿病:RAS阻滞剂+ CCB或利尿剂(推荐等级IA)
- 冠状动脉疾病: $\beta$ -blocker (BB)或CCB+ RAS阻滞剂(IA);
- 慢性肾病(CKD): RAS阻滞剂+ CCB或利尿剂(循环利尿剂[D]);
- 脑血管疾病:RAS受体阻滞剂+ CCB或D (IA);
- 房颤(AF): BB和/或非二氢吡啶CCB (IIaB);
- Hf(r/p\*EF): RAS阻滞剂+ BB、利尿剂+抗醛固酮(IA) (\*IIaB);
- 慢性阻塞性肺病:RAS阻滞剂+ CCB;
- 下肢动脉疾病:RAS阻滞剂+ CCB或利尿剂(可考虑\*BB);
- 黑人 ( Blacks ) :D + CCB (IB)。

RAS : 肾素-血管紧张素系统  
CCBs : 钙离子拮抗剂  
 $\beta$ -blocker :  $\beta$ 受体阻滞剂  
CKD : 慢性肾病  
AF : 房颤

使用钙离子拮抗剂(CCBs)后，中风、主要心血管事件、全因死亡均显著降低



## ——钙离子拮抗剂的作用



- CCBs可作为高血压治疗的第一步药物，可作为单药治疗，也可与其他药物联合治疗

- CCBs几乎可以与每一类抗高血压药物联合使用，临床的灵活性使其在日常临床实践中得到广泛应用

高血压相关的最常见的靶器官损害（TOD）是左心室肥厚(LVH)，血

- 管紧张素受体阻滞剂(ARBs)、血管紧张素转换酶抑制剂(ACE-Is)和CCBs是逆转LVH的最佳选择，可减轻TOD，减轻高血压的负担

高血压相关的常见TOD是终末期肾病，CCBs对肾小球出球和入球小

- 动脉有很强的血管扩张作用，可以降低肾小球内压，对高血压患者的肾功能有益

1. Barrios V, Escobar C, Calderon A et al. Cardiovascular risk profile and risk stratification of the hypertensive population attended by general practitioners and specialists in Spain. The CONTROLRISK study. J. Hum. Hypertens. 21(6), 479–485 (2007).
2. Messerli FH, Ketelhut R. Left ventricular hypertrophy, an independent risk factor. J. Cardiovasc. Pharmacol. 17, S59–S66; discussion S66–S67 (1991).
3. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am. J. Med. 115(1), 41–46 (2003).
4. Klag MJ, Whelton PK, Randall BL et al. Blood pressure and end-stage renal disease in men. N. Engl. J. Med. 334(1), 13–18 (2006).



1

新的指南强调了对高血压患者监测的重要性。所有成年人至少要进行一次高血压筛查，并定期复查

2

新指南着重强调了测量血压的替代方法，如动态血压监测和家庭血压测量(HBPM)。

3

建议所有高血压患者在静止时进行脉搏触诊，以了解心率，并发现是否存在心律失常和房颤

4

为了治疗高血压和CV疾病的所有潜在危险因素，建议仔细监测实验室检测结果。

5

新的指南包括建议对疑似高血压紧急患者进行诊断并对难治性高血压的诊断提出了具体的建议

6

与旧指南一样，新指南的高血压分期是根据血压水平、心血管(CV)危险因素的存在、高血压介导的器官损害(HMOD)、合并症等因素



根据新指南报道的启动药物治疗的血压阈值SBP $\geq$ 140mmHg，几乎所有患者均适用。但80岁以上的患者除外，其阈值与旧版指南相同

所有患者的降压目标值为 $<$ 140/90mmHg，若耐受大部分患者血压应 $<$ 130/80mmHg或更低。

目前推荐的药物包括五类降压药。新指南提出改善血压最有效的循证治疗策略包括联合治疗、单片复方制剂(也可作为起始治疗)和应用简单的治疗算法

随访是重中之重，做好随访可以提高患者的治疗依从性，初始降压药物治疗后2个月内至少进行1次回访，目的是评估降压效果和可能发生的不良反应；随访应持续至血压达标，并在3个月和6个月时对血压达标情况进行再次确认；

单片复方制剂治疗应在第1-2周显示降压疗效，并且血压在随后2个月内持续降低；在3个月和6个月时验证血压控制效果

至少每2年内进行危险因素和靶器官损害评估



## ——乐卡地平的作用机制

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].

- 乐卡地平属于第三代CCBs，在平滑肌细胞膜上具有较高的血管选择性和持久性。
- 第一代钙离子通道(如硝苯地平和非洛地平)会造成反射性心动过速;因此，对这些药物进行了修改，以延长作用时间和减少副作用(较长的血浆半衰期)。

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].

- 乐卡地平作用于L型和T型钙通道，对肾小球出球和入球小动脉有很强的血管扩张作用，从而降低肾小球内压。
- T型和L型钙通道可以调节血管平滑肌张力和心肌细胞，有助于心脏起搏和传导。

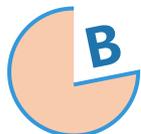


## ——乐卡地平的临床疗效

➤ 通过大量的临床研究，乐卡地平临床疗效评价总结如下：



乐卡地平联合其他抗高血压药物（无论与哪种药物联用）的降压效果均优于单一用药(p值始终 $<0.05$ )；与其他抗高血压药物联合使用简便、安全



乐卡地平联合血管紧张素转换酶抑制剂或血管紧张素II受体阻滞剂可显著降低空腹血糖和血清甘油三酯水平



乐卡地平在糖尿病和肾功能损害患者中显示出肾脏保护作用，可显著降低微量白蛋白尿，改善肌酐清除率



在乐卡地平20mg治疗的蛋白尿患者的反复研究中，结果显示，患者蛋白尿的减少速度和程度都比用乐卡地平10mg治疗的患者快，说明存在剂量依赖性



乐卡地平可以持续改善血压和蛋白尿



乐卡地平通过作用于L型和T型钙通道，对肾小球入球和出球小动脉都有很强的血管舒张作用，从而减轻肾小球高血压，发挥肾脏保护作用



## ——乐卡地平的优势特点

01

### 乐卡地平耐受性良好

不会引起明显的心率变化

02

### 乐卡地平安全性良好

不良事件发生率和退出治疗率非常低。即使不良事件的发生率在不同的研究中有所不同，但由于不良事件而停止乐卡地平治疗的比例非常低(1-2%)

03

### 乐卡地平具有最高的T/L选择性

与传统CCBs活性差异的原因在于，乐卡地平具有同时抑制L型和T型钙通道的能力。而所有二氢吡啶CCBs只能阻断>50%的L型钙通道。乐卡地平已经证明可以同时阻断L型和T型钙通道

04

### 乐卡地平具有更好的治疗依从性

市场上乐卡地平有两种剂型(10mg和20mg)，有助于满足严重高血压患者的治疗需要，20mg的配方治疗更方便



1

乐卡地平的潜在优势非常符合新的ESC/ESH指南的建议

2

乐卡地平具有全新独特的作用机制，与其他抗高血压药物联合使用简便、安全

3

乐卡地平有两种剂型，可满足重度高血压患者的治疗需要；具有良好的耐受性，可以提高治疗的依从性

4

乐卡地平是第三代钙离子拮抗剂，与其他钙离子拮抗剂相比，不良事件发生率低，可用于高危靶器官损害患者和老年人

5

在现有的治疗方案中，钙离子拮抗剂（CCBs）在降压治疗中至关重要，它们的灵活性使其在有特定医疗需求的患者中广泛使用



A

未来的高血压管理应针对每个患者进行调整，以最大限度地提高临床效益和治疗的依从性

B

为了在临床实践中实现高血压的控制，应该规划教育项目，在最初管理高血压患者的全科医生中宣传当前指南的观点和包括乐卡地平在内的新型药物的潜在优势

C

在难治和难以管理的高血压患者的治疗中，乐卡地平发挥了重要作用。乐卡地平是第三代CCBs，其特点是相对于其他CCBs，不良事件发生率低。考虑到合并症的发生率和患者的年龄，安全性和高耐受性将逐渐成为选择治疗方法的决定因素。



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