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A Discrepancy: Calcium Channel Blockers Are Effective for the Treatment of Hypertensive Left Ventricular Hypertrophy but Not as Effective for Prevention of Heart Failure

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Highlights of the Study

- Calcium channel blockers are the first-line antihypertensive drugs.
- Hypertension can lead to heart failure by causing hypertensive left ventricular hypertrophy.
- Calcium channel blockers are recommended for the treatment of hypertensive left ventricular hypertrophy.
- Calcium channel blockers protect from heart failure less effectively than other first-line antihypertensive drugs.
- This discrepancy needs to be explored further to improve clinical practice.

Keywords
Calcium channel blockers · Arterial hypertension · Left ventricular hypertrophy · Heart failure · Renin-angiotensin-aldosterone system

Abstract
Arterial hypertension (HTN) is important due to its high prevalence, morbidity, and mortality rates. Calcium channel blockers (CCBs) are the first-line antihypertensive drugs. HTN can lead to heart failure (HF) by causing hypertensive left ventricular hypertrophy (HTN LVH). CCBs are recommended for the treatment of HTN LVH. The aim of this study was to analyze the status of CCBs regarding (1) HTN LVH treatment and (2) capability to prevent HTN-induced HF in the guidelines. For this narrative review, the following databases were searched: Medline, Scopus, Science Direct, Springer, SAGE, Wiley, Oxford Journals, Cambridge, and Google Scholar. CCBs are effective antihypertensive drugs and a very good therapeutic option for HTN LVH as they can cause reverse LVH remodeling. Consequently, we may expect that CCBs would prevent HF. However, evidence suggests that CCBs confer less protection from HF than other first-line antihypertensive drugs. A negative inotropic action of nondihydropyridine CCBs may contribute to suboptimal protection against HF. This discrepancy is clinically relevant because

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CCBs are in one of the two recommended (single pill) combinations for the initial treatment of HTN. LVH is a strong risk factor for HF in HTN patients. When LVH arises, the risk of HF increases dramatically**.** CCBs are inferior to renin-angiotensin-aldosterone system blockers but still very effective in bringing about regression of HTN LVH; consequently, CCBs are expected to protect from HF. On the contrary, CCBs protect from HF less effectively than other first-line antihypertensive drugs. This discrepancy needs to be investigated further to improve clinical practice.

Introduction

Arterial hypertension (HTN) is an important public health challenge [1], due (among other reasons) to its high prevalence, estimated to be 1.13 billion patients worldwide [2]. Despite such importance, current HTN control is suboptimal [1]. Calcium channel blockers (CCBs) are among the first-line antihypertensive drugs [3]. Comprehensive initial treatment for the majority of HTN patients includes a combination of two antihypertensive drugs, for example, renin-angiotensin-aldosterone system (RAAS) blocker (angiotensin-converting enzyme [ACE] inhibitor and angiotensin receptor blocker [ARB]) with either CCB or diuretic [1, 4]. Moreover, for the treatment of hypertensive left ventricular hypertrophy (HTN LVH), CCBs are recommended (i.e., adequately believed to improve prognosis) [1], but they offer less protection from heart failure (HF) (i.e., reasonably expected to worsen prognosis) [1]. The aim of the paper was to analyze this discrepancy because CCBs are the first-line treatment of HTN (the key cause of mortality and morbidity in the world), and both HTN LVH and HF are prevalent and dangerous complications of HTN.

Literature Search

A narrative review is used for this study. The following databases were searched: Medline, Scopus, Science Direct, Springer, SAGE, Wiley, Oxford Journals, and Cambridge (Fig. 1). The Google Scholar search engine was used in addition. Particular attention was paid to guidelines related to systemic HTN.

Results

Hypertension Is a Crucial Risk Factor for HF

HTN is the main attributable risk factor for HF [5]. HTN precedes the development of HF in approximately 90% of patients and increases the risk for HF by 2- to 3-fold [6, 7]. Moreover, HTN is the crucial risk factor for coronary artery disease (CAD) [7, 8], which is responsible for a great number of HF patients [7, 9]. Therefore, HTN can lead to HF directly by causing HTN LVH and can subsequently lead to HF with preserved left ventricular ejection fraction (HFpEF) [10, 11], and this pathway is common in elderly women [12]. Moreover, HTN can cause HF indirectly through CAD (particularly myocardial infarction) [11, 13]. This happens more often in men, and such patients usually have HF with reduced left ventricular ejection fraction [13]. HF with reduced left ventricular ejection fraction may arise from HFpEF when a "second hit" occurs (acute myocardial infarction, myocardial toxins, such as alcohol, cocaine, medications, etc.) [7]. The main benefit of antihypertensive drugs is the prevention of HF [5].

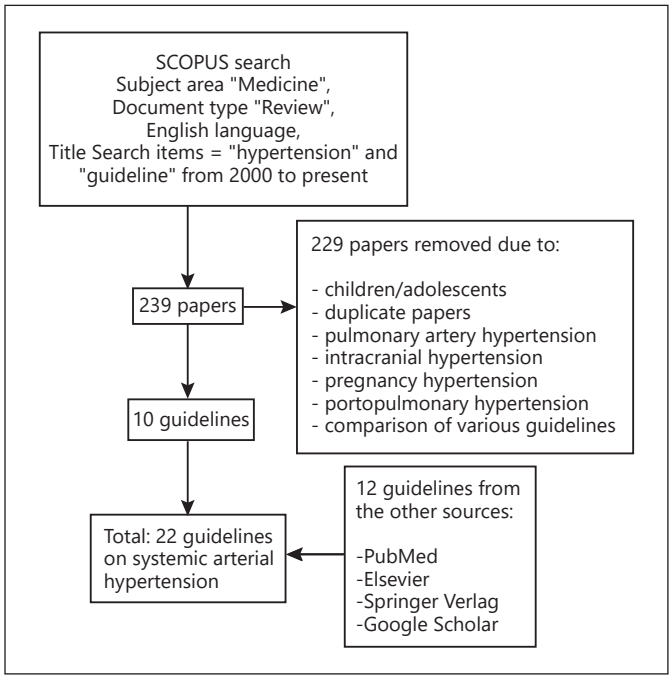

Fig. 1. Depiction of search strategy.

HTN LVH Is an Even More Direct and Important Precursor of HF

LVH is very prevalent in HTN (36–41% by echocardiography) [14, 15]. Among HTN patients, those with HTN LVH are at particularly high risk [16, 17]. The mortality risk is more than twice increased in individuals with LVH [18]. The risk of atrial fibrillation (AF) is 39% high-

Table 1. Compelling indications for CCBs (among other indications).

CCBs	Indications	References
(1) Dihydropyridine subclass	Stable angina pectoris (chronic coronary syndrome)	[26, 29–31]
	Diabetes mellitus	[28]
	Previous stroke	[28]
	Vasospastic angina pectoris	[32]
	Hypertensive left ventricular hypertrophy	[3]
	HTN in elderly mostly (isolated) systolic HTN	[26, 29]
	HTN in pregnancy	[28, 29]
	Peripheral arterial disease	[26, 29]
	(Isolated) systolic hypertension	[26]
	Carotid atherosclerosis	[26, 29]
	Coronary atherosclerosis	[26]
	High coronary risk	[6]
(2) Nondihydropyridine subclass	Paroxysmal, persistent, or permanent AF	[1]
	Supraventricular tachycardia	[26, 29, 33]
	Effort, vasospastic, and unstable AP	[3, 26, 29, 30]
	Persistent proteinuria in diabetic kidney disease	[34]
	High coronary risk	[6, 26, 29]
	Carotid atherosclerosis	[29]

CCBs, calcium channel blockers; HTN, arterial hypertension; AP, angina pectoris.

er in these patients [19], and AF is a well-recognized risk factor and trigger of HF [20]. HTN LVH often precedes HFpEF [10, 21]. The occurrence of ventricular tachycardia/fibrillation is 2.8-fold greater in the presence of LVH [22]. The presence of LVH is also associated with a 4.5-fold increased risk for sudden cardiac death [18].

CCBs Are Effective for Arterial Treatment of Hypertension

CCBs are effective antihypertensive medications [1, 3, 23–27]. Moreover, in recommendations on how to start treatment of HTN patients without compelling indications for other antihypertensive drugs, CCBs are one of a few drug classes, together with diuretics and RAAS blockers [28] and, according to some guidelines, β-blockers (BBs) as well [1]. Older age favors the use of CCBs [29]. Compelling indications for CCBs are listed in Table 1. The favorable characteristics of CCBs are that these agents are more effective compared to most other antihypertensive drugs in reducing proteinuria as well as in slowing the progression of carotid atherosclerosis [1]. CCBs are associated with improved results in preventing stroke [35–38]. In addition to this, CCBs are well tolerated by the general hypertensive population [1, 39].

CCBs Are Very Effective for Treating LVH

LVH as hypertension-mediated organ damage is a marker and/or mediator of ischemic heart disease, HF, arrhythmias, and sudden cardiac death [5]. The reversal of LVH by antihypertensive drugs significantly reduces the risk for cardiovascular events [40, 41]. The magnitude of reversal of LVH reversal is in direct correlation with reduction in blood pressure (BP) [1]. ACE inhibitors, ARBs, and CCBs are more effective than BBs and diuretics in bringing about regression in LVH [42, 43]; interestingly, the beneficial effects of RAAS blockers on cardiac and electrophysiological left ventricular remodeling seem to be independent of reduction in BP [44]. On the other hand, there are some inter-class differences between diuretics in the magnitude of reversal of HTN LVH [45]; some BBs can diminish the risk of ventricular arrhythmia in patients with LVH [46]. Mineralocorticosteroid receptor antagonists, although not first-line antihypertensive drugs, have a similar beneficial effect on LVH as ACE inhibitors [47]. Also, angiotensin receptor neprilysin inhibitor as one of the four pillars of HF therapy has a great impact on LVH reversal [48, 49].

In addition to good results in the general hypertensive population, CCBs are also very good for a subset with HTN LVH therapy [1, 3, 15, 39, 50]. CCBs can cause reverse remodeling (i.e., decreasing wall thickness) of the

Table 2. HTN guidelines' citation about CCBs' favorable effects toward LVH reverse remodeling and unfavorable actions provoking HF in the SAME relevant guidelines.

HTN guideline/expert consensus document/clinical policy title	CCBs beneficial for HTN LVH	CCBs precipitate HF	DHP- or non-DHP-CCBs precipitate HF	Reference number
(1) Seventh report of the Joint national committee on prevention, detection, evaluation, and treatment of high blood pressure	Yes	Yes	Amlodipine in ALLHAT trial	[6]
(2) Latin America expert group. Latin American guidelines on hypertension	Yes	–	–	[54]
(3) Dutch guideline for the management of hypertensive crisis – 2010 revision	–	–	–	[55]
(4) ACCF/AHA 2011 expert consensus document on hypertension in the elderly: A report of the American college of cardiology foundation task force on clinical expert consensus documents	In general, RAAS blockers should be preferred in elderly patients with HTN LVH.	HF as an adverse effect	HF as an adverse effect	[11]
(5) 2013 ESH/ESC guidelines for the management of arterial hypertension	Yes	Still an open question, the largest meta-analysis confirms it, but there are methodological issues. Nevertheless, CCBs in HTN population decrease new-onset HF by ~20% versus placebo	–	[5]
(6) American College of Emergency Physicians Clinical Policies Committee. Clinical policy: critical issues in the evaluation and management of adult patients in the emergency department with asymptomatic elevated blood pressure	–	–	–	[23]
(7) 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8)	–	To improve HF outcomes, either diuretic or ACEi is better than CCB.	–	[24]
(8) South African hypertension practice guideline 2014	–	–	–	[29]
(9) Guideline for the diagnosis and management of hypertension in adults – 2016	–	Yes	–	[56]
(10) 7th Brazilian Guideline of Arterial Hypertension: Chapter 14 – Hypertensive Crisis. Arq Bras Cardiol. 2016 Sep; 107 (3 Suppl 3):79–83. doi: 10.5935/abc.20160164				[57]
(11) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults	Yes	In preventing HF, the thiazide diuretic is superior to the CCB.	Amlodipine is inferior to the chlorthalidone in preventing HF.	[25]
(12) Kenya National Guidelines For Cardiovascular Diseases Management. 2018	–	–	–	[58]
(13) Management of Hypertension in the SESLHD Ward Settings. 2018	–	–	–	[59]
(14) 2018 Chinese Guidelines for Prevention and Treatment of Hypertension	LVH is a strong indication for CCB	–	–	[26]
(15) Academy of Medicine of Malaysia. The Clinical Practice Guidelines (CPGs); Management of Hypertension (5th Edition) 2018	–	–	–	[60]
(16) 2018 ESC/ESH Guidelines for the management of arterial hypertension	Yes, better than BBs	Yes, CCBs protect less from HF versus diuretics and RAAS blockers	–	[1]

Table 2 (continued)

HTN guideline/expert consensus document/clinical policy title	CCBs beneficial for HTN LVH	CCBs precipitate HF	DHP- or non-DHP-CCBs precipitate HF	Reference number
(17) ESC Council on hypertension position document on the management of hypertensive emergencies	–	–	–	[61]
(18) The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019)	Yes	–	–	[3]
(19) 2019 Chinese guideline for the management of hypertension in the elderly	Yes	–	–	[62]
(20) Brazilian Position Statement on Hypertensive Emergencies – 2020	–	–	–	[63]
(21) Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children	Yes	–	–	[64]
(22) Synopsis of the 2020 U.S. Department of Veterans Affairs/U.S. Department of Defense Clinical Practice Guideline: The Diagnosis and Management of Hypertension in the Primary Care Setting	–	Yes	–	[65]

HTN, arterial hypertension; CCBs, calcium channel blockers; LVH, left ventricular hypertrophy; ALLHAT, the antihypertensive and lipid-lowering treatment to prevent heart attack trial; RAAS, renin-angiotensin-aldosterone system; HF, heart failure; ESC/ESH, the European Society of Hypertension (*ESH*) and the European society of cardiology (*ESC*).

LV; this is important because the reduction of LVH during antihypertensive treatment is associated with a better prognosis [3, 51, 52]. One meta-analysis showed that CCBs are better than BBs and diuretics in LV reverse remodeling [42]. Thus, CCBs are recommended in relevant guidelines on HTN for HTN LVH [1]. Moreover, they can inhibit abnormal gene expression of contractile proteins, atrial natriuretic polypeptide, and collagens and presumably prevent an increase in myocardial stiffness which results in cardiac dysfunction [53]. Table 2 summarizes several relevant guidelines.

HTN LVH Is an Important Precursor of HF and an Indication for CCBs; CCBs Are Expected to Prevent HF, but CCBs Protect from HF Less than Other First-Class Antihypertensive Drugs

A well-known indication for CCBs is HTN LVH [15], a well-known risk factor of HF [7]. Consequently, we may expect that CCBs would prevent HF by successful treatment of HTN LVH; however, this is not the case. CCBs protect from HF less effectively than other first-class antihypertensive drugs [35–37, 66, 67]. An explanation for this is still unclear. A negative inotropic action of nondihydropyridine CCBs may contribute to suboptimal protection against HF (lesser than that of other first-line antihypertensive drugs) [1]. This discrepancy is clinically relevant because CCBs are in one of the two recommended (single pill) combinations for the initial treatment of the majority of the HTN population (without a compelling indication for a specific antihypertensive drug) [1].

Discussion

The relationship between CCBs and suboptimal HF prevention is recognized by guidelines; the consequences (including costs) are named "astronomical" in one paper [68]. Hypertension has a major population-attributable risk for HF; it is as high as 59% in females and 39% in males [69]. LVH is a strong risk factor for HF in HTN patients [6]. When LVH arises, the risk of HF increases dramatically [7]. Therefore, what makes HTN LVH more severe, for example, uncontrolled HTN, also leads further to HF [68]. Likewise, what protects from HTN LVH or decreases (reverses) already present LVH is also expected to protect from HF, for example, good BP control [70]. Moreover, the Systolic Blood Pressure Intervention Trial (SPRINT) concluded that intensive BP control (target systolic BP <120 mm Hg) results in lower rates of development of new LVH compared with standard BP control

(target systolic BP <140 mm Hg) [71]. Furthermore, reversal of LVH in those patients who had already developed LVH was more common in the intensive BP group compared with group that had BP <140 mm Hg for target [71]. In line with this, primary HF prevention depends strongly on decrease in BP [72]. CCBs diminish HTN LVH and are anticipated to protect from HF; unexpectedly, this is not demonstrated in trials. On the contrary, several trials demonstrated an increased risk of HF with use of CCB; for example, patients treated with verapamil had incident HF 30% more than with diuretic in the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial [73]. Moreover, there was 37% less HF with valsartan versus amlodipine [74] and 38% higher with amlodipine versus diuretic [75]. A recent meta-analysis encompassed 80,483 patients from 18 randomized clinical trials (with an average follow-up of 51.4 months) and demonstrated a 25% increased risk of HF with the use of intermediate-acting CCB from dihydropyridine subgroup [36]. Consequently, HTN guidelines pay attention to this topic and warn that CCBs are less protective against HF in comparison with other first-line antihypertensive drugs [1]. Indeed, we ought to separate acute from chronic effects. Negative inotropic action of non-DHP CCBs is pronounced and can be the trigger of acute decompensation. For example, we reported a patient with normal LV systolic function who had new-onset (paroxysmal) AF with rapid ventricular rate, who was treated with verapamil i.v., and this finally resulted in acute cardiogenic pulmonary edema [76]. This negative inotropic effect seems to be responsible partially for the increased HF incidence in HTN patients on CCBs. It can be (even more) evident with the co-occurrence of other risk factors of acute HF, including excessive salt intake, use of nonsteroidal anti-inflammatory drugs, infection, or AF.

Finally, one should have in mind that the reduction of systolic BP for 10 mm Hg or diastolic BP for 5 mm Hg reduces the risk of HF for 40% [1]. The more important objective of HTN treatment is prevention of HF and other cardiovascular diseases/events rather than beneficial effect on LVH reverse remodeling.

Conclusion

CCBs are the mainstay of treatment of numerous diseases, including the initial therapy of HTN (in combination with RAAS inhibitor). Moreover, RAAS inhibitors and CCBs can reverse LVH remodeling better than BBs and diuretics. As HTN LVH precipitates HF, RAAS blockers and CCBs are consequently expected to protect from HF. This is true for RAAS blockers; on the contrary, CCBs protect less from HF than other first-line antihypertensive drugs. Further research is required to explain this discrepancy.

Statement of Ethics

All authors have adhered to institutional and generally accepted ethical standards. The research was conducted ethically following the guidelines of the World Medical Association Declaration of Helsinki.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript.

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Author Contributions

Goran Koracevic and Zoran Perisic: study concept and design; Goran Koracevic, Zoran Perisic, and Maja Stanojkovic: drafting of the manuscript. All authors contributed to literature review, interpretation of data, and critical revision of the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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