Calcium Channel Blockers in Cardiovascular Pharmacotherapy

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Abstract

This paper summarizes the pharmacological properties of calcium channel blockers (CCBs), their established therapeutic uses for cardiovascular disorders and the current improvement of their clinical effects through drug combinations. Their identification resulted from study of small molecules including coronary dilators, which were named calcium antagonists. Further experiments showed that they reduced contraction of arteries by inhibiting calcium entry and by interacting with binding sites identified on voltage-dependent calcium channels. This led to the denomination calcium channel blockers. In short-term studies, by decreasing total peripheral resistance, CCBs lower arterial pressure. By unloading the heart and increasing coronary blood flow, CCBs improve myocardial oxygenation. In long-term treatment, the decrease in blood pressure is more pronounced in hypertensive than in normotensive patients. A controversy on the safety of CCBs ended after a large antihypertensive trial (ALLHAT) sponsored by the National Heart, Lung, and Blood Institute. There are two main types of CCBs: dihydopyridine and non-dihydropyridine; the first type is vascular selective. Dihydropyrines are indicated for hypertension, chronic, stable and vasospastic angina. Non-dihydropyridines have the same indications plus antiarrythmic effects in atrial fibrillation or flutter and paroxysmal supraventricular tachycardia. In addition, CCBs reduced newly formed coronary lesions in atherosclerosis. In order to reach recommended blood pressure goals, there is a recent therapeutic move by combination of CCBs with other antihypertensive agents particularly with inhibitors acting at the level of the renin-angiotensin system. They are also combined with statins. Prevention of dementia has been reported in hypertensive patients treated with nitrendipine, opening a way for further studies on CCBs' beneficial effect in cognitive deterioration associated with aging.

Introduction

The identification of calcium channel blockers (CCBs) resulted from an analytical pharmacology project in my laboratory aiming at describing the biological characteristics of small molecules named in the early 1960s such as adrenolytics, cholinolytics, histaminolytics, or coronary dilators. Those drugs were used for various indications, some of them for angina pectoris. Lidoflazine was the first of a series of drugs identified as coronary dilators[1]; they also included verapamil,[2] nifedipine,[3] and diltiazem.[4] We studied the inhibition of the contraction of vessels evoked by several agonists including norepinephrine, serotonin, vasopressin, acetylcholine, and angiotensin. Because inhibitions by lidoflazine in a given preparation looked similar to other inhibitors,[5] it was concluded that lidoflazine and other inhibitory agents should interfere with a mechanism similarly activated by the constrictors. We hypothesized that this mechanism would involve the translocation of calcium (Ca) that is required to support smooth muscle contraction.[6-9] This hypothesis was tested in isolated arteries by examining how the various inhibitors so far identified blocked the contraction supported by Ca in depolarized arteries. In view of the experimental results, these inhibitors were named "calcium antagonists."[10] Fleckenstein et al coincidentally made use of this term in their study of the role of Ca in cardiac contraction in relation to use of high-energy phosphates and to oxygen consumption.[11,12] Experimental studies provided the demonstration that the most specific Ca antagonists inhibited Ca entry through voltage-operated Ca channels, allowing the terminology calcium entry blockers and a more appropriate one: calcium channel blockers (CCBs), when their binding to voltage-operated Ca channels had been demonstrated to be responsible for their pharmacological effects.[11,13,14]

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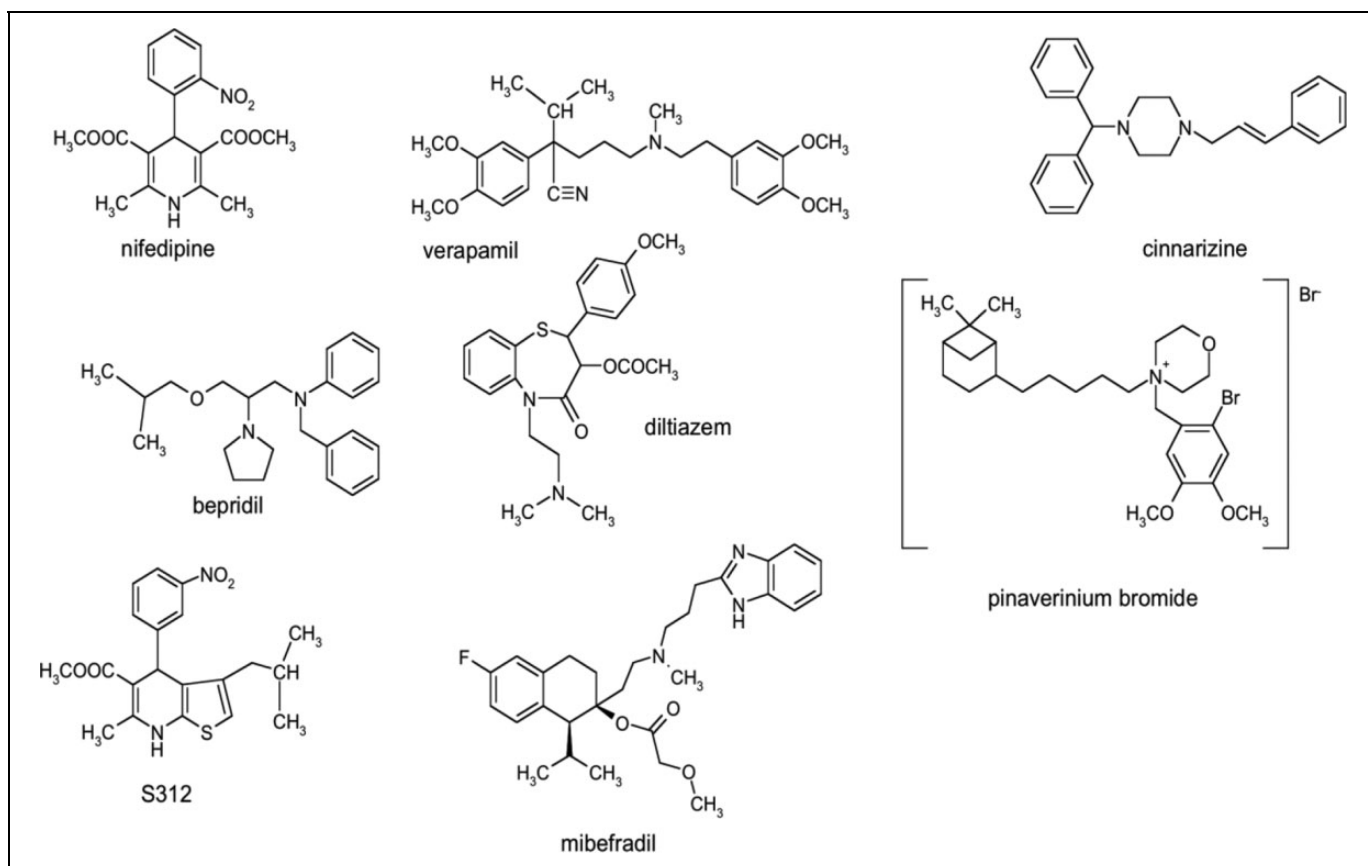Email: theophile.godfraind@uclouvain.be

Figure 1. Lead compounds of calcium channel blockers. Note the structures diversity, a basis for interaction with various binding sites on calcium channel subunits and for different ratios of affinity between the dissimilar types of voltage-dependent calcium channels from Godfraind.[34]

Box 1. CCBs marketed in Western countries and in Japan

Amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and verapamil. Of these, diltiazem, isradipine, nicardipine, nifedipine, and verapamil have both immediate and extended-release formulations available (ranging from 1 to 4 times daily), felodipine and nisoldipine have only extended-release formulations (given once daily), and amlodipine is long-acting drug available as immediate release only (given once daily). Lacidipine, lercanidipine, and cilnidipine are not marketed in the United States. Nimodipine (Nimotop) is only indicated for subarachnoid hemorrhage.

In this article, I will provide a brief account of the pharmacological characteristics of CCBs, a description of their established therapeutic use for cardiovascular (CV) disorders, and finally the current improvement in their clinical effect through drug combinations.

Pharmacological Characteristics of CCBs

As mentioned earlier, the discovery of CCBs resulted from an analytical pharmacology project in my laboratory designed to analyze the pharmacological characteristics of either small molecules named in the early 1960s, antispasmodics, adrenolytics, cholinolytics, histaminolytics, or coronary dilators. Those drugs were used for various indications, some of them for angina pectoris. We studied the response of isolated vessels to vasoconstrictors in the presence of recognized inhibitors. The drugs studied were the plant alkaloid papaverine, derivatives from the phenothiazine group such as chlorpromazine, derivatives from the diphenylpiperazine group such as lidoflazine and cinnarizine, and derivatives of the dihydropyridine group such as nifedipine. The initial study was extended to several dihydropyridines, to diltiazem, and to verapamil. We observed that each of these inhibitors blocked at a same concentration the contractile response of isolated arteries to different stimulants including norepinephrine, vasopressin, angiotensin, and serotonin. This blocking effect could not be reported on the basis of the receptor theory, which implies that antagonists are specific for a given agonist. Therefore, we hypothesized that those blockers should prevent a process involved in translocation of activator Ca^{2+} following receptor activation. The Ca fraction activating the contractile machinery could have been translocated from either the outside of the cell or an intracellular store.[15-18] Therefore, the action of those blockers was examined on an epinephrine-evoked contraction of arterial smooth muscle bathed either in the presence or in the absence of Ca in the tissue perfusion fluid.
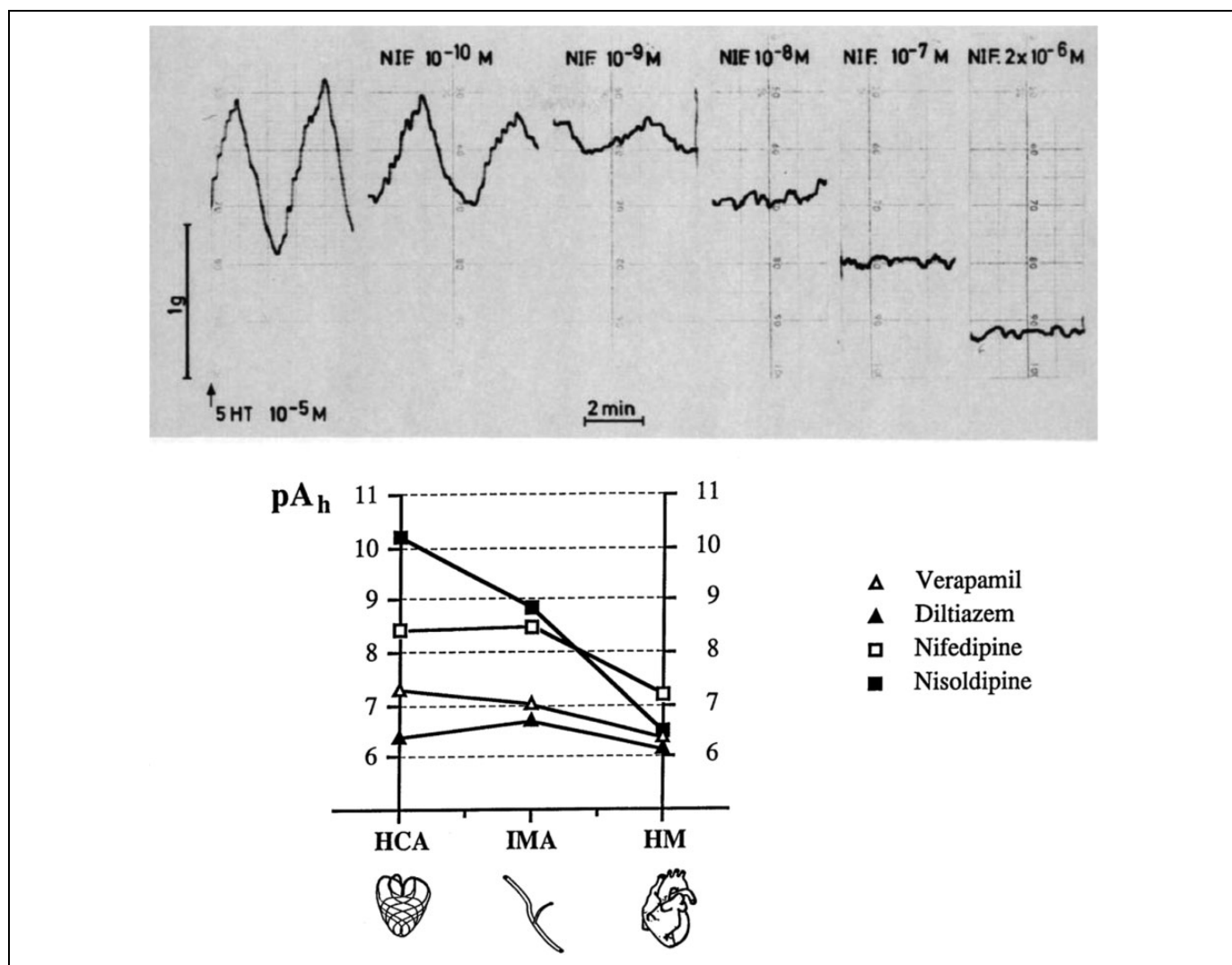
Figure 2. Calcium channel blockers (CCBs) on contraction of human coronary arteries and of human cardiac muscle. Upper panel, Action of increasing concentrations of nifedipine on the contractile activity evoked by serotonin (5HT) 10^{-5}mol/L in isolated segment of human coronary artery (HCA). Serotonin was added at the arrow, and maintained or the duration of the observation, modified from Godfraind et al.[29] Lower panel, pAh values (log $1/IC_{50}$) IC_{50} is the inhibitory concentration 50 of CCBs indicated on the graph in the human coronary artery (HCA) and the human internal mammary artery (IMA), both being stimulated by serotonin and the human myocardium (HM). Modified from Godfraind et al.[31]

Blockade of the contraction was apparent in the presence of a physiological concentration of Ca^{2+} but not on the reduced contraction evoked in the absence of extracellular Ca^{2+}. This observation indicated that blockers jammed Ca movement from outside to inside the smooth muscle cell activated by a vasoconstrictor.[9] Various experiments have been performed to better characterize this inhibitory effect and to localize the cellular target of this action. At first, we examined the influence of Ca^{2+} on the contraction of isolated arteries bathed in a depolarizing solution either without or with a given blocker. These experiments demonstrated that either diphenylpiperazines or dihydropyridines blocked the contraction evoked by extracellular Ca in depolarized arteries by displacing to the right Ca dose-effect curves. The graphical representations of these experiments resembled those obtained in agonist–antagonist studies. This observation prompted the denomination Ca antagonist.[10] In a series of experiments performed on Ca fluxes during vessels stimulation, we noticed that Ca antagonists reduced the rate of Ca influx. Inhibitions of Ca influx and of contraction were superimposed, indicating that inhibition of tonic contraction of vessels resulted from inhibition of Ca entry suggesting the denomination Ca entry blocker. The specific binding of Ca entry blockers was located with voltage-dependent Ca channels in the plasmalemmal membrane of the smooth muscle cell.[19-21] Therefore, those drugs were renamed calcium channel blockers (CCBs)[14] (Figure 1 and Box 1). The denomination Ca channel antagonist is also used by a few authors.[22,23] Voltage-operated Ca channels
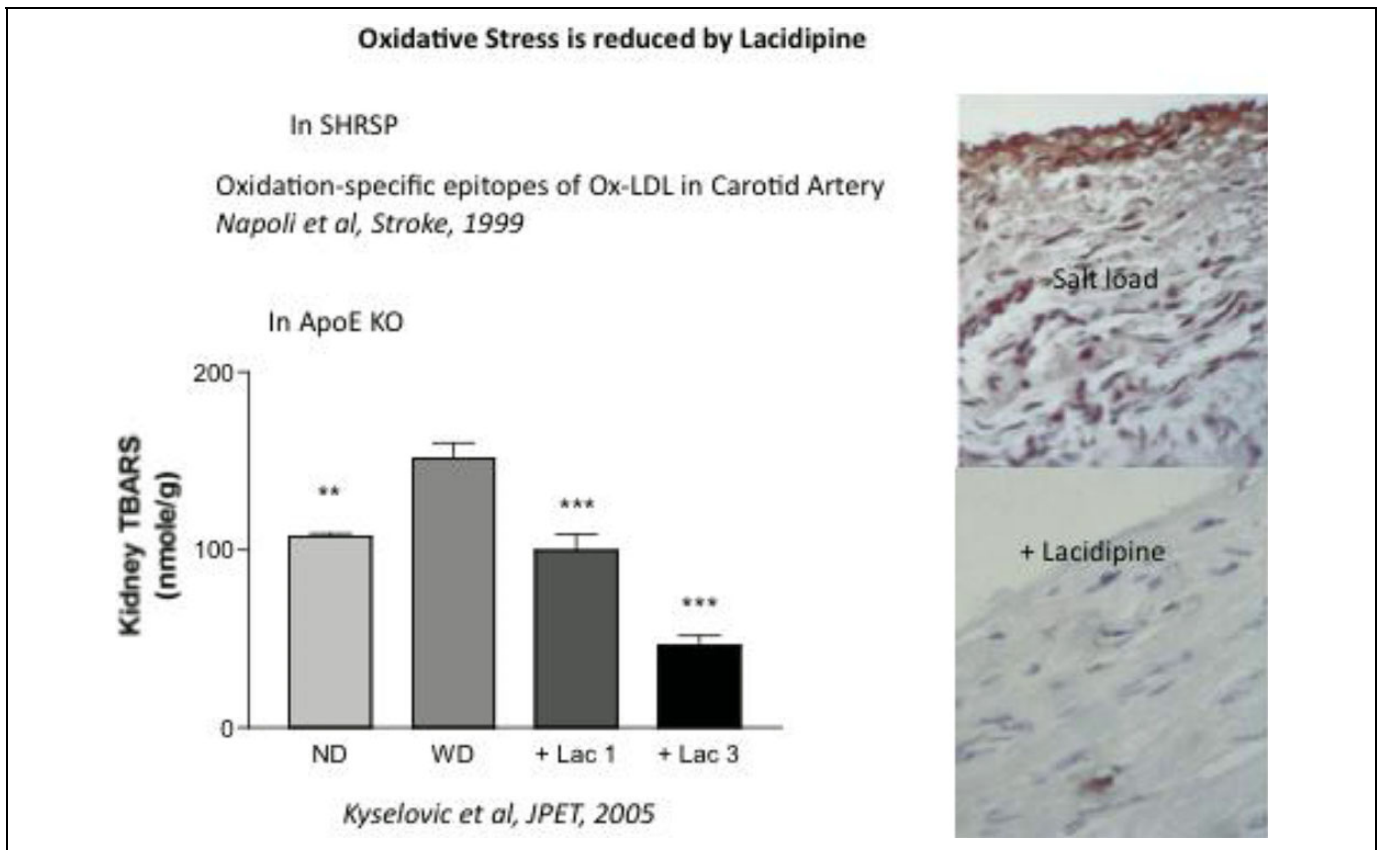
Figure 3. Illustration of the antioxidant capacity of calcium channel blocker (CCB). Right panel, Illustration by the action of lacidipine (1 mg/kg/d) on the abundance of oxidized low-density lipoprotein (LDL) identified in the arterial intima of rat carotid artery by specific antibodies; epitopes recognized by the primary antibody are brown, and the nuclei are counterstained with hematoxylin. Sections of carotid artery from the salt-loaded SHRSP control group and from the group treated with lacidipine. Modified from Napoli et al.[35] Left panel, Kidney thiobarbituric acid-reactive substances (TBARS) content, marker of oxidative stress. There was a significant difference in kidney TBARS content between apolipoprotein E[-/-]mice on normal diet (ND) and Western-type diet (WD) mice; the augmentation was dose dependently prevented by lacidipine (1 or 3 mg/kg); data from Kyselovic et al.[36]

exhibit different biochemical, electrophysiological, and pharmacological properties. A classification is based on distinct voltage-operated Ca^{2+}currents[24] recognizing L-, N-, T-, P-, Q-, and R-types. It is consistent with the biochemical classification.[25,26] Classification of drugs into dihydropyridine and nondihydropyridine type is not only academic since these 2 types of molecules interact at distinct sites on voltage-operated Ca channels and display great differences in vascular versus cardiac actions[27-30] (Figure 2).They also show dissimilar ratio of blockade of T- and L-types Ca channels that are distributed among the cardiovascular system.

In short-term studies, by decreasing total peripheral resistance, CCBs lower arterial pressure. Short-acting compounds might elicit abrupt vasodilatation. The expected physiological response should be tachycardia and increased cardiac output accompanying reflex augmentation of plasma catecholamines. This can elicit angina and even acute myocardial infarction as was reported in early clinical trials with short-acting compounds.[32] These acute changes are not observed with the long-acting compounds.[32] Negative inotropic effect, diminution of sinus node automaticity,

conduction slowing in the atrioventricular node, and little, if any, effect on the automaticity of the myocytes have been reported, but the effects are less important with dihydropyridines such as isradipine, felodipine, amlodipine, nisoldipine, lacidipine, and cilnidipine than with nondihydropyridine CCBs like verapamil and diltiazem. By unloading the heart, increasing coronary blood flow, and reducing myocardial oxygen consumption, long-acting CCBs generally improve myocardial oxygenation.[14]

Decrease in blood pressure (BP) is the most apparent consequence of the long-term blockade of L-type Ca channels. This decrease is more pronounced in patients with hypertension than in normotensive individuals.[33] This indicates that CCBs are not only vasodilators but that they may be also considered as specific antihypertensive agents. Potential mechanisms involved in their long-term action on elevated BP and contributing to their therapeutic effects comprise antioxidant effects[34,35] (Figure 3), inhibition of endothelin-1 synthesis[37,38] and effects on vascular contractility and cardiac hypertrophy,[39-42] interaction with nitric oxide production and action,[43,44] prevention of endothelial dysfunction,[37,45] of cardiac remodeling in hypertension,[46] of stroke,[47] and antiatherosclerotic action.[36]

Table 1. Calcium Channel Blockers Currently Marketed in the United States.

Drug	Proprietary Name	Indications, United States	Form; Dose	Elimination half-life, h
Amlodipine	Norvasc	Hypertension; chronic, stable, and vasospastic angina	Tablet: 2.5, 5, 10 mg; once daily	30-50
Diltiazem	Tiazac; Cardizem; Cartia; Dilacor	Hypertension; chronic, stable, and vasospastic angina; atrial fibrillation or flutter; paroxysmal supraventricular tachycardia	Immediate release (IR), controlled release (CR), and IV; 180-540 mg: once daily	IR: 2-5; CR: 2.5
Felodipine	Plendil	Hypertension	CR: 2.5, 5, 10 mg; once daily	11-16
Isradipine	Dynacirc	Hypertension	Tablet: 2.5, 5 mg;once daily	8-12
Nicardipine	Cardene	Hypertension; angina	IR tablet: 20, 30 mg; 3 times daily	8
Nifedipine	Adalat; Procardia	Hypertension; angina	CR capsule: 30, 60, 90 mg; once daily	2
Nisoldipine	Sular	Hypertension	SR tablet: 10, 20, 30, 40 mg; once daily	7-12
Verapamil	Calan; Covera; Verelan	Hypertension, angina; atrial fibrillation or flutter; paroxysmal supraventricular tachycardia	IR tablet: dose on indication; CR: 120-360 mg; once daily	4.5-12

Box 2. Adverse effects

Non-dihydrpyridines. Diltiazem and verapamil tend to inhibit drug metabolism. This enzyme inhibitory effect is a potential source of drug interactions, for example, with cyclosporin. When used with β-blockers, care must be taken for bradycardia and atrioventricular conduction delay due to direct cardiac effects. Constipation with verapamil is a common side effect. *Dihydropyridines.* Possible headache and flushing are due to peripheral vasodilation as well as tachycardia and palpitation secondary to reflex activation of the sympathetic nervous system. Swelling of ankles and occasionally hands due to disturbance of hemodynamics of microcirculation (preferential precapillary arteriolar vasodilation). Pedal edema is one of the most common adverse effects of calcium antagonists. It has been observed with all available dihydropyridine agents, but it also seems to occur to a lesser extent with verapamil and diltiazem. The incidence of pedal edema is clearly dose dependent and may exceed 80% with very high doses of dihydropyridine CCB. As mentioned subsequently, it may be reduced with drug combinations. Gum hypertrophy is a rare effect.

Classical Key Knowledge About CCBs in Therapy

An early paradigm was that some CV dysfunctions resulted from reduced tissue perfusion. Therefore, the therapeutic indications of CCBs were initially based on their relaxing effect on constricted arteries and additionally on their antiarrhythmic action. Later, it was proposed that additional long-term effects supported their use in the management of CV disturbances.[14]

The Controversy on the Safety of CCBs

The CCBs controversy was caused by an influential meta-analysis published[48] in 1995. The authors of this meta-analysis concluded that in patients with coronary heart disease

(CHD), the use of the short-acting nifedipine in moderate to high doses caused an increase in total mortality, which questioned the safety of CCBs in therapy. Several authors have opposed the conclusions of this meta-analysis.[32,49,50] The controversy ended after the publication of results and subgroup analysis of a large antihypertensive trial named the Anti-Lipid Lowering Heart Attack Trial (ALLHAT) that was sponsored by the National Heart, Lung, and Blood Institute.[51-53] In more than 30 000 high-risk patients with hypertension, it compared the CCB amlodipine, the angiotensin converting-enzyme (ACE) inhibitor (ACEI) lisinopril, and the diuretic chlorthalidone, respectively, on CHD. The primary end point consisted of the combination of fatal CHD and acute myocardial infarction. In the trial, no differences occurred in their incidence. The ALLHAT study prompted a large series of analytical and commentary papers. The analysis of prespecified subgroups by Leenen et al[54] highlighted the importance of ALLHAT findings for the management of patients with hypertension, which currently represent 20% to 30% of the world's population. Analysis of Leenen et al was in agreement with randomized control trials (RCTs) of which the Coronary disease Trial investigating Outcome with Nifedipine GITS (GASTROINTESTINAL THERAPEUTIC SYSTEM) (ACTION) trial is a good example of the therapeutic effect of CCBs.[55] The ACTION trial was designed to study clinical outcomes in 7665 patients with a mean age of 63.5 years (3825 nifedipine; 3840 placebo) with stable angina and left ventricular (LV) ejection fraction of at least 40% and requiring oral or transdermal treatment either to treat or to prevent anginal attacks. In a mean follow-up of 4.9 years, investigators randomly assigned patients to addition of either nifedipine GITS at a starting dose of 30 mg once daily increased to a maintenance dose of 60 mg once daily or matching placebo to the basic regimen that they were taking. Between the 2 groups, there was no significant difference in CV events and death rates. The ACTION trial extended with nifedipine GITS the safety conclusions obtained from ALLHAT with amlodipine. At the present time, the controversy *on the safety of CCBs* is closed.

The Therapeutic Indications of CCBs

Eight CCBs are currently marketed in the United States, which have CV indications and adverse effects depending on the specific drug as reported in Table 1 and Box 2. The CCB-based treatment of stable angina and use of nondihydropyridine CCBs for treating supraventricular arrhythmias are conventional practices. However, CCBs are not recommended in case of systolic dysfunction. In consideration for the use of CCBs in hypertension, the just published 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)[56] is closer to the Clinical Guidelines 127 of the National Institute for Health and Clinical Excellence (NICE 127) than was the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[57] It appears now that the medical community at large is reaching a consensus based on evidence in recommending CCBs in initial treatment of hypertension. For instance, NICE Clinical Guidelines 127 (http://www.nice.org.uk/CG127) support CCB treatment of people aged more than 55 years and of black people of any age. It favors combination with a diuretic in patients with diabetes but does not recommend CCBs in heart failure. The American Heart Association (AHA), the American College of Cardiology (ACC), and the Centers for Disease Control and Prevention Science Advisory by Go et al[58] provides an algorithm that, as mentioned by the authors, should not be used to counter the treating health care provider's best clinical judgment.

In reference to a meta-analysis comparing effectiveness within CCBs,[59] there is no clinical evidence for dissimilarity in therapeutic effectiveness of the various dihydropyridine-type CCBs. However, others[60] reported a crossover study of amlodipine versus nifedipine based on home BP monitoring via cellular phone. They noted that amlodipine had a lower antihypertensive effect than nifedipine during the critical morning period but with a lesser morning pulse rate. More head-to-head clinical studies are required to draw any comparative conclusion in order to extend or not to extend experimental findings of patients with hypertension from experimental studies on human tissues.[28,61]

Calcium Channel Blockers and β-blockers

In the 1970s, it was reported that agents other than nitrates efficiently treat stable angina. The β-blockers have preceded CCBs in that respect; therefore, several trials with CCBs such as verapamil and nifedipine have attempted to evaluate their relative efficiency by comparison with propranolol as well as their action over placebo. The criteria usually adopted in order to assess the efficacy of the drugs were the following[14]:

(1) decrease in nitroglycerin consumption;
(2) reduction in the frequency of anginal episodes;
(3) prolongation in exercise time;
(4) increase in work capacity;
(5) ST recovery time, measuring myocardial ischemia following exercise by the duration of ST depression;
(6) degree of ST depression at a defined workload, providing the demonstrated reproducibility of this depression.

Results of RCTs confirmed the efficacy of β-blockers and CCBs and could not indicate difference in their antianginal effects. According to a recent review,[62] evidence is robust for the anti-ischemic effect of β-blockers and CCBs. Are there bases for choosing one of them versus the other in the management of angina? Lionel Opie[63] discussed the relative choice of β-blockers and of CCBs in stable effort angina. He noted that safety problems occurred with β-blockers. For instance in an observational study over 6 years on 12 550 patients with hypertension, those taking CCBs had no increase in developing diabetes, whereas those treated with β-blockers available at that time had a 28% higher risk. He added that the choice could depend both on the patient and on the heart. The quality of life must be preserved in an active middle-aged man by considering that exercise training and sexual function are important. Therefore, there are good arguments for prescribing a CCB. He pointed out that when angina is associated with hypertension, dihydropyridine CCBs and β-adrenergic blocking agents are similarly effective. The 2012 American College of Cardiology Foundation, American Heart Association, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease (SIHD) provides an algorithm for guideline-directed medical therapy for patients with SIHD.[64] A comprehensive list of recommendations is available in the document. Accessible information is also obtainable from W. H. Frishman's article on β-adrenergic blockade in CV disease published in *Journal of Cardiovascular Pharmacology and Therapeutics*.[65]

This last statement should be revisited in view of Anglo Scandinavian Cardiac Outcome Trial (ASCOT)[66] and European Lacidipine Study on Atherosclerosis (ELSA)[67] trial comparing CCB-based treatment to a β-blocker-based regimen. These trials showed a better protection with CCB than with β-blocker for a similar reduction in BP. However, there is a rationale for combining a β-blocker-based regimen and CCBs for angina when looking for a better control of heart rate. ASCOT[66] was a multicenter, prospective, RCT in 19 257 patients with hypertension aged 40 to 79 years with at least 3 other CV risk factors. Investigators defined BP targets (mm Hg < 140/90, but < 130/80 if diabetes) and allocated either amlodipine 5 to 10 mg adding perindopril 4 to 8 mg when required (amlodipine-based regimen; n = 9639) or atenolol 50 to 100 mg adding bendroflumethiazide 1.25 to 2.5 mg and potassium when required (atenolol-based regimen; n = 9618). Nonfatal myocardial infarction (including silent myocardial infarction) and fatal CHD were the primary end points. The amlodipine-based regimen induced less diabetes and prevented more major CV events than the atenolol-based regimen. According to the authors, this might not be entirely explained

by better control of BP. The ELSA is discussed subsequently under atherosclerosis.

Calcium Channel Blockers in Cardiac Arrhythmias

Nondihydropyridine CCBs (nd-CCBs) display antiarrhythmic effects due to blockade of Ca current generating slowly propagating action potentials that occur in slow response tissues such as sinoatrial and atrioventricular nodes. Ventricular myocardium and Purkinje fibers, which are fast conducting tissue, may be converted by acute myocardial infarction into slow response tissue. Indeed, in ischemic areas increased intracellular sodium (Na) concentration and decreased intracellular potassium concentration cause partial depolarization in resting cells and slowed Na channel reactivation so favoring slow Ca currents. The slow depolarizing rate is responsible for decrement slowing of conduction velocity. Conduction blocks can occur in different regions of the heart (sinus node, AV node, His Purkinje system, and contractile myocardium) and play an essential role in the development of reentrant pathways. The reentry mechanism is usually involved in the occurrence of premature beats and ventricular tachycardia. To be initiated, both unidirectional block of conduction and slow conduction must happen. An anatomical and functional barrier may exist and form a circuit. Arrhythmias that result from such circus movements are self-sustained but are not self-initiated. They can be initiated by a single premature stimulus.

In 1971, it was reported that verapamil (still considered at that time as a β-blocker) exhibited powerful antiarrhythmic action by reducing the ventricular rate in atrial fibrillation.[68] This has stimulated interest for this drug and also for the other agents ranged later in class IV antiarrhythmics.[69] If verapamil and diltiazem appear to be powerful antiarrhythmic agents in vivo, this is not the case for dihydropyridines that usually evoke reflex tachycardia. Reflex increase in sympathetic tone could overcome a slight negative chronotropic effect due to dihydropyridines.

The action of verapamil and diltiazem has been well documented in supraventricular tachycardia. Intravenous verapamil is efficient for the acute conversion of reentrant supraventricular tachycardia. Diltiazem is slightly less effective than verapamil. Those nondihyropyridine CCBs are more efficacious than cardiac glycosides and propranolol. However, chronic prophylaxis of paroxysmal supraventricular tachycardia with verapamil given per os (80-120 mg three times daily) has not been quite convincing,[70,71] but it is recommended in the European Society of Cardiology (ESC) guidelines.[72] In atrial fibrillation, intravenous injection of verapamil and diltiazem produces a reduction in the ventricular response and may tend to regulate the ventricular response.[71] In the VErapamil plus antiarrhythmic drugs reduce atrial fibrillation recurrences after an electrical cardioversion (VEPARAF) study,[73] particularly in older patients, it was observed that the addition of verapamil to amiodarone or flecainide significantly reduced the atrial fibrillation recurrences in patients who underwent electrical cardioversion. In patients with recurrence within 3 months after cardioversion, verapamil reduced the secondary atrial fibrillation recurrences.

However, verapamil and diltiazem are not indicated for patients with atrial fibrillation or flutter, complicating the Wolff-Parkinson-White syndrome with anterograde conduction through the bypass tracts. In the presence of anomalous bundle, verapamil and diltiazem are contraindicated because they may accelerate the ventricular response; a treatment by catheter ablation is recommended in the ESC guidelines for the management of atrial fibrillation.[72]

Calcium Channel Blockers in Hypertension

Calcium channel blockers have been proposed as antihypertensive drugs on the basis of their potent vasodilator properties. In vivo, they appear to act mainly on the arterial bed. They reduce the vascular resistance (and afterload) and evoke a reduction in BP. In agreement with animal experiments, the reduction is much greater in patients with hypertension than in normotensive individuals.[33] A similar observation has been reported with other CCBs including verapamil, nitrendipine, diltiazem, tiapamil, and isradipine but not with propranolol or captopril.[74] Experimental studies have shown that vessels of hypertensive rats have a higher affinity for CCBs than vessels of normotensive ones. This increased affinity is likely responsible for the higher sensitivity of patients with hypertension to the effect of CCBs when compared to normotensive controls.[75] Their efficacy in patients with low renin activity is believed to be one of the determinants for their action in patients whose hypertension is insensitive to β-blockers. In contrast to a pronounced arteriolar effect, no significant venous relaxation has been found after CCBs administration. This is consistent with an absence of orthostatic hypotension in patients treated with those drugs. The interaction of CCBs with the renin–angiotensin system is complex as observed in animal experiments.[46] Calcium channel blockers exhibit a natriuretic effect. This action has been shown to occur without substantial alteration in renal plasma flow or in glomerular filtration rate.[76,77] The natriuretic action justified the use of CCBs in monotherapy of hypertension. It is masked during prolonged treatment but may be revealed by a fall in natriuresis observed after drug withdrawal.

Long-term administration of CCBs to spontaneously hypertensive rats protects the heart against pathological remodeling and is also able to induce substantial regression of established LV hypertrophy and to improve cardiac function.[46] The prospective randomized enalapril study evaluating regression of ventricular enlargement (Preserve) trial[78] compared the cardiac effects of CCBs and of ACEIs in patients with hypertension having LV hypertrophy. This trial was designed to primarily test the hypothesis that enalapril induced greater regression of LV hypertrophy than nifedipine, despite equivalent BP reduction. Treatment began with 10 mg enalapril or 30 mg nifedipine GITS and matching placebo. Over l2-week titration phase, enalapril or nifedipine could be, respectively, increased to 20 mg or 60 mg. Hydrochlorothiazide (HCTZ; 25 mg) and then atenolol (25 mg) were recommended when maximum dose did not control BP. More supplemental treatment with

HCTZ was required in ACEIs-treated patients than in CCB-treated patients. The most important result of the study is that both regimens significantly reduced to the normal range LV mass index and relative wall thickness during 1 year of treatment in about 50% of patients. There was no significant difference in LV mass index between the 2 treatment regimens. Regression or prevention of hypertrophy in patients was initially attributed to normalization of BP and LV systolic load. However, the beneficial effect of CCBs might involve several mechanisms including reduction in elevated BP, blunting of hypertrophic gene activation in myocardial and vascular cells as a consequence of long-term inhibition of Ca entry, protection against renal damage and the subsequent activation of the RAS, and, possibly, reduction in oxidative stress in CV tissues.[79] These 2 latter mechanisms of action may take a variable part in the CV protection evoked by individual CCBs.

The reduction by BP lowering of the incidence of stroke and myocardial infarction has been demonstrated in clinical trials. Direct comparisons among the various types of antihypertensive agents are limited but in agreement with ASCOT,[80] meta-analyses[81] indicated that CCBs offer the best protection against stroke and myocardial infarction. It does not follow from small differences in mean BP between groups (of about 2 mm Hg) that CCBs protection might be attributed to effects independent of BP reduction as this was the case in experimental animal.

Diabetic nephropathy causes end-stage renal disease. It is characterized by albuminuria, elevated BP, and a persistent loss of renal function. Adequate control of BP is delaying the progression of renal disease in diabetic patients. Among CCBs, verapamil and efonidipine (not marketed in United States) have been reported to be as efficient in this pathology.[82] Studies of renal vasculature showed that efonidipine dilates the efferent artery while nifedipine dilates predominantly afferent artery.[83] This might be due to an action on T-type Ca channels[84] similar to the verapamil one when amlodipine and nifedipine are weak blockers of those channels.[26] A role for amlodipine in renal disease is reported subsequently under Combination Therapies with CCBs.

Calcium Channel Blockers in Atherosclerosis

Several studies have shown that raised plasma lipid levels constitute an important risk factor for arteries, and clinical evidence suggests that sustained lipid-lowering therapy can inhibit the progression of the disease. Clinical studies have been designed in order to examine whether a similar clinical result could be achieved with CCBs that do not influence plasma lipid levels. Rationale for those clinical trials came from experimental studies in animals. Animal experimental studies were confirmed by the international Nifedipine trial on antiatherosclerotic therapy (INTACT).[85] This trial showed that nifedipine significantly reduced the appearance of newly formed coronary lesions in patients. In contrast, arteriograms did not detect modification in progression or regression of existing lesions over 3 years, once fibrosis and calcification had begun. Risk factors were similar and no statistically significant

differences were evident in the relative frequencies of unstable angina, nonfatal myocardial infarction, and the need for revascularization between the treated and the untreated patients. However, experience gained from studies with lipid-lowering procedure indicates that significant clinical advantage is unlikely to become apparent until treatment has been continued for 5 to 7 years. Furthermore, the role of reduction in BP in atherosclerosis was not evaluated by INTACT when nifedipine was studied against a placebo.

As pointed out earlier, long duration seems to be required in order to characterize an action of CCBs over other antihypertensive agents. A support to this hypothesis is provided by the the Verapamil in Hypertension and Atherosclerosis Study (VHAS).[86] It compared verapamil (240 mg once a day) and chlorthalidone (25 mg once a day). Blood pressure-lowering effect of the 2 randomized treatments was similar, but CV events had a greater incidence in patients randomized to chlorthalidone ($P < .05$), despite small differences in carotid wall changes between chlortalidone and verapamil-treated patients. The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT)[87] was designed to test whether amlodipine would slow the progression of early coronary atherosclerosis. By comparison with placebo, amlodipine had a significant effect in slowing the 36-month progression of carotid artery atherosclerosis but neither on angiographic progression of coronary atherosclerosis nor on risk of major CV events. Nevertheless, it was associated with fewer hospitalizations for unstable angina and revascularization. Other randomized trials confirmed that CCB compared to diuretic reduced progression of carotid lesions in patients.[88,89] However differences were small. Therefore, on the basis of animal experimental data showing differences in CCBs pharmacological action, clinical trials with various molecules are justified. The ELSA trial had this purpose.[67] It compared carotid intima-media thickness (IMT) changes over 4 years in patients receiving the dihydropyridine lacidipine versus the β-blocker atenolol. Compared to atenolol-treated patients, lacidipine-treated ones exhibited greater protection of carotid IMT progression and number of new plaques increase, in spite of a smaller BP reduction. This indicates that the antiatherosclerotic action of lacidipine might be, at least partly, independent of the lowering of BP.

A Therapeutic Move: Combination Therapies With CCBs

In order to reach recommended BP goals, instead of increasing the dose of a given agent, using more than 1 drug makes more therapeutic sense, as a mixture of therapeutic agents from different classes with different modes of action might cover more than 1 etiology. Antihypertensive monotherapy could not address the multifactorial nature of hypertension, a disease with many pathways. Systematic combinations have been initiated by trials such as ASCOT in which perindopril 4 to 8 mg was added to amlodipine-based regimen when required in order to reach recommended BP goal. This initiated an interesting

therapeutic move such as the introduction of combination of CCBs with other antihypertensive agents, particularly with agents acting at the level of RAS including ACEI or angiotensin receptor antagonists (ARBs). This has prompted the launch of fixed combinations, which improve quality of life and treatment compliance.[90] In patients who did not reach recommended response to one component only, the additive or synergistic effect of combination therapy evoked increased lowering of BP. Recent clinical trials on combination therapy are summarized subsequently.

Combination of CCB With ARB

Dual Combination

Randomized controlled clinical trials allowed observation that combination with CCBs of other antihypertensive drugs evoked an augmented reduction in BP when compared with monotherapy. This was demonstrated in various clinical trials; one recent trial studied amlodipine and olmesartan.[91] This 8-week multicenter trial was conducted at 172 sites in the United States. Patients were randomized to 1 of 12 treatment regimens: monotherapy or combination with amlodipine (5 or 10 mg/d) and olmesartan medoxomil (OLM; 10, 20, or 40 mg/d). This included a stratification based on age, race, diabetes status, and baseline BMI.

Efficacy. Efficacy variables were the change from baseline in mean seated diastolic pressure (SeDBP) and seated systolic pressure (SeSBP) at week 8. Combination evoked greater reduction in BP than monotherapy except in blacks in who amlodipine alone evoked a higher percentage of patients with BP achievement than did the combination. The best combination was amlodipine 10 mg + olmesartan 40 mg/d.

Tolerability. Treatment-emergent adverse events (TEAEs) reported comprised edema, hypotension, headache, and dizziness/vertigo. Safety variables were recorded at all visits. No marked differences were observed in the safety profile obtained in the various patient subgroups. However, in contrast to BP data, edema data were not shown in all conditions. Therefore, this efficacy and tolerability study did not provide information on a potential correlation between reduction in BP and incidence of TEAEs.

Community Outreach and Cardiovascular Health Study

The Community Outreach and Cardiovascular Health (COACH) study[92] was a comparison between OLM (10, 20, or 40 mg) and amlodipine besylate (AMLO; 5, 10 mg), during 8 weeks monotherapy and various combinations in randomized patients who had a SeDBP of 95 to 120 mm Hg. Significant reductions in SeDBP from baseline were noted in all groups (P < .001). The greatest reduction occurred in the groups that had received combination therapy. There were no apparent differences in the overall incidence of TEAEs across treatment groups, and the majority of adverse events were considered mild in severity. The most common TEAE was edema, occurring at

baseline in 264 (13.6%) of 1940 patients. It increased during treatment up to 385 (19.8%) of 1940 patients. The frequency of edema was greatest in patients receiving monotherapy with AMLO 10 mg (36.8%) and was lowered in patients in which AMLO 10 mg was combined with OLM. This reached statistical significance relative to AMLO 10 mg in the groups that received OLM ± AMLO 20/10 mg (P = .032) and 40/10 mg (P = .011). These observations indicate that edema was not related to decrease in BP, but that it was depending on the dose of AMLO and that AMLO-dependent edema was reduced by OLM.

Open-Label Extension Trial. The Open-Label Extension (OLE) trial illustrated the continuing effect of combination therapy of OLM and AMLO by showing that the efficacy of the combination was maintained long term in 67% of the 1684 patients treated with AMLO 10 mg + OLM 40 mg.[93] Indeed the reduction in BP after 52 weeks amounted to 29.4 mm Hg, a value close to the one recorded in the COACH trial after 8 weeks (28.5 mm Hg). In order to achieve BP goal (<140/90 or <130/80 mm Hg if diabetic), HCTZ 12.5 or 25 mg had been used in the 33% of other patients. This observation is in agreement with others.[94]

Triple Combination

Triple combination has been proposed for patients who did not quickly attain BP goals with dual combination (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes or chronic kidney disease). Hydrochlorothiazide 12.5 or 25 mg has been used in various trials, including OLE discussed earlier in order to achieve BP goal. This was based on the complementary mechanisms of action of agents.

Calhoun et al reported results of a trial of the combination AMLO ± valsartan (Val) ± HTZ in patients with hypertension (mean SeSBP: ≥145 mm Hg; mean SeDBP: ≥100 mm Hg).[95] The study included 4 groups of patients; each received one of the following combinations: AMLO/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, AMLO/Val 10/320 mg, or AMLO/HCTZ 10/25 mg once daily. Triple therapy was significantly superior to all of the dual therapies in reducing BP (P < .0001) and in achieving overall BP control (<140/90 mm Hg; P < .0001). The combination of AMLO/Val/HCTZ was well tolerated regardless of age, sex, race, and ethnicity.

Phase III Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study (TRINITY) is another randomized clinical trial studying a cohort of 2492 patients treated with OLM 40 mg + AMLO 10 mg + HCTZ 25 mg compared with OLM 40 mg/AMLO 10 mg, OLM 40 mg/HCTZ 25 mg, and AMLO 10 mg + HCTZ 25 mg in patients who had a mean SeBP ≥ 140/100 mm Hg or ≥160/90 mm Hg.[96] After 12 weeks, the triple combination treatment was significantly more efficient than dual ones (P < .001) and about 70% of patients reached BP targets of <140/90 mm Hg compared with about 50% to 40% in the dual combinations (P < .001). The occurrence of TEAEs was roughly similar to the 2 trials discussed earlier. The highest value occurred for edema with the combination of AMLO + HTZ (9.8% in

TRINITY and 8.9% in the Calhoun trial) and was reduced with triple therapy, respectively, down to 7.7% and 4.5%.

All sartans could not offer equipotent combinations with amlodipine as claimed by Fogari et al[97] who reported that Val 160 mg + amlodipine 5 mg evoked greater BP decrease than losartan 100 mg + amlodipine 5 mg. A limitation of the study of Fogari is that the trial did not provide a monotherapy comparison on the efficacy of the 2 sartans. However, Elliott et al[98] conducted a trial comparing losartan 50 mg with Val 80 mg showing a similar reduction in BP. If this comparison could be extended to double doses, then Fogari et al could be right.

Various Combinations With Antihypertensive Agents

Calcium channel blockers have been combined with antihypertensive agents other than recent ARBs which included thiazide diuretics, β-blockers, and ACEIs. Interest in combinations with those 3 groups was illustrated by RCTs performed some years ago and are supported by more recent meta-analyses that justified the marketing of fixed combinations.[99]

Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension Trial.
Although current guidelines recommend inclusion of a diuretic, the optimal combination drug therapy for hypertension is not yet established. Indeed, there are scarce comparisons between combinations. Therefore the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial is of great interest.[100] During 42 months, it compared benazepril (an ACEI) + amlodipine to benazepril + HCTZ (a thiazide diuretic). When only considering BP, the 2 combinations looked similar. However, the primary end point of this trial was not the level of BP reduction but the reduction in the rate of cardiovascular events, which was superior with benazepril + amlodipine to benazepril + HCTZ.

Other combinations have been studied including ACEIs such as perindopril + amlodipine in the ASCOT trial.[66] The ASCOT[66] was a multicenter, prospective, RCT in 19 257 patients with hypertension aged 40 to 79 years with at least 3 other CV risk factors. Investigators defined BP targets (mm Hg < 140/90 mm Hg, but < 130/80 mm Hg if diabetic) and allocated either amlodipine 5 to 10 mg adding perindopril 4 to 8 mg when required (amlodipine-based regimen; n = 9639) or atenolol 50 to 100 mg adding bendroflumethiazide 1.25 to 2.5 mg and potassium when required (atenolol-based regimen; n = 9618). Nonfatal myocardial infarction (including silent myocardial infarction) and fatal CHD were the primary end points. The amlodipine-based regimen induced less diabetes and prevented more major CV events than the atenolol-based regimen. According to the authors, on the basis of previous trial evidence, these effects might not be entirely explained by better control of BP. A literature search in PubMed identifying 2 recent trials was published in the Russian language. Authors examined cerebrovascular parameters in patients with hypertension. On the basis of their abstracts, it appears that the effect of amlodipine + indapamide was superior to the effect of indapamide + bisoprolol (a β-blocker) or lisinopril (ACEI).[101] In another abstract, it was claimed that impairment of disturbances of cerebral blood flow was better improved by verapamil + enalapril than by verapamil + indapamide.[102]

Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation Trial.
The Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial has been revaluated by Chalmers et al[103] in order to assess how CCBs influenced the effects of a fixed combination of perindopril and indapamide in patients with type 2 diabetes mellitus. The analysis of patients enrolled in ADVANCE was based on the nature of the basic treatment for hypertension prescribed before the fixed combination treatment. Of the 11 140 patients enrolled in ADVANCE trial, 3427 were taking a CCB and represented a higher risk group. The triple combination provided a further protection against all-cause mortality and hard CV outcomes in those patients when compared to the dual fixed combination. This beneficial action of CCBs could not be attributed to a specific agent since this question was not answered from the trial.

OlmeSartan and Calcium Antagonists Randomized Trial.
Novel dihydropyridines are under examination in Japan. The Olme-Sartan and Calcium Antagonists Randomized (OSCAR) trial[104] combined amlodipine or azelnidipine plus olmesartan. The authors concluded that olmesartan + CCB was more efficient in lowering BP and reducing the incidence of major hypertension complications than was monotherapy even with high dose of olmesartan. Results in OSCAR publication do not make the distinction between the 2 CCBs. This is most unfortunate since amlodipine and azelnidipine have a different pharmacological profile, particularly at the level of the renal circulation.[105]

Quantitative Analysis of the Increased Response Induced by Combination

Quantitative analysis of the increased response to drug combinations has been studied in the meta-analyses. An extensive one choosing 42 publications out of a preliminary screening of 1697 articles covering a total of 10 698 participants aimed to quantify the results of the combinations.[106] The 42 randomized factorial trials addressed thiazides, β-blockers, ACEIs, or CCBs using each class of drug separately or in combination with the specified drug class. Angiotensin-II receptor blockers (ARBs) were not incorporated in the meta-analysis because of being considered too new class of drug. Authors calculated the mean BP reductions in each trial as the reduction in the treated group minus that in the placebo group. They expressed the dose of each drug in each trial as a multiple of the standard dose. Therefore, they followed Law et al[107] who considered that the standard dose is the usual maintenance dose recommended in reference pharmacopoeias.

In this meta-analysis, authors did not consider individual drug but the drug class as a single entity. The mean doses of the

drugs in the selected trials were usually close to the standard. The results from this meta-analysis showed that the BP reduction was an additive process when each class of drug was combined with 1 from another class. For instance, considering CCB used alone, they observed that after subtracting the mean placebo reduction in systolic BP, the reduction for the standard CCB dose was equal to 8.4 mm Hg and that for the combination with another class evoking a BP reduction of 7.5 mm Hg, it was equal to 14.3 mm Hg, a value that was not significantly different from the sum of the 2 individual effects. The reduction was equal to 11.6 mm Hg by doubling the CCB standard dose. Thus, the combination of CCB with other classes of drug resulted in an additive effect that was more effective than doubling the dose. However, this analysis did not consider potential differences in therapeutic efficacy of the various chemical entities belonging to a given pharmacological class. Other conclusions could result from a more specific analysis.

Combination of CCB With Statin

As shown earlier, it has been established in several animal studies and RCTs that CCBs exert a therapeutic effect on atherosclerosis. The lowering of cholesterol concentrations by statins in individuals reduces the risk of CV disease. This is illustrated by the ASCOT trial. The purpose of ASCOT[66] was to assess and compare the effects of atenolol with or without a diuretic versus amlodipine with or without an ACEI on nonfatal myocardial infarction and fatal CHD in patients with hypertension. From the ASCOT-Blood Pressure Lowering Arm (ASCOT-LLA) trial,[80] it appeared that the primary prevention of CHD was improved by cholesterol lowering in patients with hypertension under BP therapy. The ASCOT-LLA data showed that atorvastatin (ATV) compared with placebo reduced primary events by 53% in the amlodipine-based group and by 16% in the atenolol-based group, P interaction = .02. The ASCOT trial is one of those justifying the use of a combination of a CCB and a statin in preventing complications of hypertension, but the problem of drug interaction needs to be considered. Indeed the plasma concentration of a statin may be dramatically increased when an isoenzyme that is essential for drug elimination is partially or completely inhibited. This is placing patients at risk of adverse events. Patients treated with statins are at risk of taking the nondihydropyridine CCBs verapamil and diltiazem, which inhibit cytochrome P450 3A4 (CYP3A4), the most predominant isoform involved in metabolism of lovastatin, simvastatin, ATV, and cerivastatin. Dihydropyridines (eg, nifedipine and amlodipine) do not have an effect on this isoenzyme. Other agents act on statin pharmacokinetics. This is the case of grapefruit juice interacting with the action of statins by inhibiting CYP3A4 in the gut wall and leading to an increase in blood level of statins and thereby in their potential toxic action. Interactions with grapefruit juice have also been shown with dihydropyridines such as felodipine and nifedipine, but it is less important with amlodipine. It should be remembered that commonly prescribed drugs inhibiting the

3A4 isoenzyme are the macrolide antibiotics (ie, erythromycin, clarithromycin, and telithromycin) and azole antifungals (ie, itraconazole and ketoconazole).

From the therapeutic point of view, it appeared that statins and CCBs exert a synergistic effect. This is observed at the level of BP: an analysis of data from the National Health and Nutrition Examination Surveys (NHANES) was performed on a total of 10 531 participants.[108] It was observed that users of antihypertensive drugs plus statins had a lower BP than users of only antihypertensive drugs, but that per se statins did not decrease BP. In order to evaluate the action of CCB plus statin combination, Martin-Ventura et al randomized 26 patients with hypertension undergoing carotid endarterectomy to receive either ATV 20 mg/d alone (ATV, n = 12) or in combination with amlodipine 20 mg/d (ATV + AMLO, n = 14) before scheduled carotid endarterectomy.[109] There was a significant difference between the 2 groups in total and LDL-cholesterol levels at the end of follow-up (4-6 weeks) but not in BP (probably due to a too low number of patients). A significant reduction in macrophage infiltration in relation to the ATV group was demonstrated by immunohistochemistry of carotid atherosclerotic plaques from ATV + AMLO group. The authors concluded that combination of ATV + amlodipine decreased inflammatory status of patients with atherosclerosis more than monotherapy with ATV. On the basis of pharmacokinetic criteria, it seems useful prescribing fixed combination of CCB with statin. The best known is CADUET,[110] which is the combination of AMLO with ATV Ca 5/20 mg; it improved adherence and BP goal attainment.

Conclusions and Perspectives

From this review on CCBs in pharmacotherapy, it is obvious that this class of drugs is efficacious for the management of hypertension and for the prevention of associated pathologies including coronary artery disease, renal failure, atheromatous CV disease, stroke, peripheral vascular disease, and heart failure. This conclusion is emphasized by a recent analysis of treatment groups of the ACTION trial showing that the lowest CV event rates were observed in those in receipt of RAS blocker + nifedipine GITS, specifically in those treated for isolated systolic hypertension.[111] The current trend in drug combination reinforces the therapeutic efficacy of CCBs as shown on the basis of BP reduction. Therefore, trials such as ADVANCE with outcomes considering CV events are expected in the light of potential CCB actions unrelated to BP effect.

Cognitive deterioration is a worldwide pathological process associated with aging.[112] Syst-Eur investigators[113] have noted that the prevalence of dementia was significantly reduced in patients with hypertension receiving nitrendipine. Randomized patients continued active study for a further period of observation. After 5 years, it was observed that this medication prevented 20 cases of dementia per 1000 patients. This indicates that the protective action of nitrendipine is a continuing effect.[114] Clinical trials are announced to test this action with other CCBs.[115]

Moreover, electrophysiological data[26] show that the ratio of inhibitory concentration 50 for blocking T- and L-type Ca channels is different within dihydropyridine-type CCBs. The therapeutic consequences of this disparity deserve consideration in view of the hypothesis that a high T–L affinity ratio provides a protective effect against nephropathy.[82] In conclusion, regarding the best management of the patient with CCBs the last statement is not yet on paper.

Declaration of Conflicting Interests

Funding

References

1. Schaper WK, Xhoneux R, Jageneau AH, Janssen PA. The cardiovascular pharmacology of lidoflazine, a long-acting coronary vasodilator. *J Pharmacol Exp Ther*. 1966;152(2):265-274.

2. Haas H. Zum wirkungsmechanismus des alpha-isoprpyl-alpha-[(N-methyl-N-homoveratridil)-gamma-aminopropyl]-3,4-dimetoxy phenylacetonitrils, einer substanz mit coronargefässerweiternden eigenschaften. *Arzneim-Forsch*. 1964;12:461-468.

3. Vater W, Kroneberg G, Hoffmeister F, et al. [Pharmacology of 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarb oxylic acid dimethyl ester (Nifedipine, BAY a 1040)]. *Arzneimittelforschung*. 1972;22(1):1-14.

4. Sato M, Nagao T, Yamaguchi I, Nakajima H, Kiyomoto A. Pharmacological studies on a new l,5-benzothiazepine derivative (CRD-401). *Arzneimittelforschung*. 1971;21(9):1338-1343.

5. Godfraind T, Kaba A, Polster P. Specific antagonism to the direct and indirect action of angiotensin on the isolated guinea-pig ileum. *Br J Pharmacol Chemother*. 1966;28(1):93-104.

6. Godfraind T, Kaba A. The role of calcium in the action of drugs on vascular smooth muscle. *Arch Int Pharmacodyn Ther*. 1972; 196(suppl 196):35-49.

7. Godfraind T, Kaba A. Inhibition by cinnarizine and chlorpromazine of the contraction induced by calcium and adrenaline in vascular smooth muscle. *Br J Pharmacol*. 1969;35(2):P354-P355.

8. Godfraind T, Kaba A, Polster P. Differences in sensitivity of arterial smooth muscles to inhibition of their contractile response to depolarization by potassium. *Arch Int Pharmacodyn Ther*. 1968;172(1):235-239.

9. Godfraind T, Kaba A. Blockade or reversal of the contraction induced by calcium and adrenaline in depolarized arterial smooth muscle. *Br J Pharmacol*. 1969;36(3):549-560.

10. Godfraind T, Polster P. Etude comparative de médicaments inhibant la réponse contractile de vaisseaux isolés d'origine humaine ou animale. *Thérapie*. 1968;23(5):1209-1220.

11. Godfraind T, Miller R, Wibo M. Calcium antagonism and calcium entry blockade. *Pharmacol Rev*. 1986;38(4):321-416.

12. Fleckenstein A. History of calcium antagonists. *Circ Res*. 1983; 52(2 pt 2):I3-I16.

13. Godfraind T. Calcium entry blockade and excitation contraction coupling in the cardiovascular system (with an attempt of pharmacological classification). *Acta Pharmacol Toxicol (Copenh)*. 1986;58(suppl 2):5-30.

14. Godfraind T. *Calcium Channel Blockers*. Basel/ Boston/Berlin: Birkhaäuser Verlag; 2004.

15. Evans DHL, Schild HO, Thesleff S. Effect of drugs on depolarized plain muscle. *J Physiol*. 1958;143(3):474-485.

16. Edman KAP, Schild HO. Interaction of acetylcholine, calcium and depolarization in the contraction of smooth muscle. *Nature*. 1961;190:350-352.

17. Edman KAP, Schild HO. Calcium and the stimulant and inhibitory effects of adrenaline in depolarized smooth muscle. *J Physiol*. 1963;169:404-411.

18. Edman KAP, Schild HO. The need for calcium in the contractile responses induced by acetylcholine and potassium in the rat uterus. *J Physiol*. 1962;161:424-441.

19. Wibo M, DeRoth L, Godfraind T. Pharmacologic relevance of dihydropyridine binding sites in membranes from rat aorta: kinetic and equilibrium studies. *Circ Res*. 1988;62(1):91-96.

20. Godfraind T, Wibo M. Subcellular localization of [3H]-nitrendipine binding sites in guinea-pig ileal smooth muscle. *Br J Pharmacol*. 1985;85(2):335-340.

21. Grover AK, Kwan CY, Luchowski E, Daniel EE, Triggle DJ. Subcellular distribution of [3H]nitrendipine binding in smooth muscle. *J Biol Chem*. 1984;259(4):2223-2226.

22. Triggle DJ. The pharmacology of ion channels: with particular reference to voltage-gated Ca2+ channels. *Eur J Pharmacol*. 1999;375(1-3):311-325.

23. Triggle DJ. Calcium channel antagonists: clinical uses–past, present and future. *Biochem Pharmacol*. 2007;74(1):1-9.

24. Nowycky MC, Fox AP, Tsien RW. Three types of neuronal calcium channel with different calcium agonist sensitivity. *Nature*. 1985;316(6027):440-443.

25. Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. *Neuron*. 2000;25(3):533-535.

26. Perez-Reyes E, Van Deusen AL, Vitko I. Molecular pharmacology of human Cav3.2 T-type Ca2+ channels: block by antihypertensives, antiarrhythmics, and their analogs. *J Pharmacol Exp Ther*. 2009;328(2):621-627.

27. Godfraind T. Calcium antagonists and vasodilatation. *Pharmacol Ther*. 1994;64(1):37-75.

28. Godfraind T, Morel N, Wibo M. Tissue specificity of dihydropyridine-type calcium antagonists in human isolated tissues. *Trends Pharmacol Sci*. 1988;9(1):37-39.

29. Godfraind T, Finet M, Lima JS, Miller RC. Contractile activity of human coronary arteries and human myocardium in vitro and their sensitivity to calcium entry blockade by nifedipine. *J Pharmacol Exp Ther*. 1984;230(2):514-518.

30. Sun J, Triggle DJ. Calcium channel antagonists: cardiovascular selectivity of action. *J Pharmacol Exp Ther*. 1995;274(1): 419-426.

31. Godfraind T, Salomone S, Dessy C, Verhelst B, Dion R, Schoevaerts JC. Selectivity scale of calcium antagonists in the human cardiovascular system based on in vitro studies. *J Cardiovasc Pharmacol*. 1992;20(suppl 5):S34-S41.

32. Opie LH, Yusuf S, Kubler W. Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. *Prog Cardiovasc Dis*. 2000;43(2): 171-196.

33. Leonetti G, Cuspidi C, Sampieri L, Terzoli L, Zanchetti A. Comparison of cardiovascular, renal, and humoral effects of acute administration of two calcium channel blockers in normotensive and hypertensive subjects. *J Cardiovasc Pharmacol*. 1982;4(suppl 3):S319-S324.

34. Godfraind T. Antioxidant effects and the therapeutic mode of action of calcium channel blockers in hypertension and atherosclerosis. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1464):2259-2272.

35. Napoli C, Salomone S, Godfraind T, et al. 1,4-Dihydropyridine calcium channel blockers inhibit plasma and LDL oxidation and formation of oxidation-specific epitopes in the arterial wall and prolong survival in stroke-prone spontaneously hypertensive rats. *Stroke*. 1999;30(9):1907-1915.

36. Kyselovic J, Martinka P, Batova Z, Gazova A, Godfraind T. Calcium channel blocker inhibits western-type diet-evoked atherosclerosis development in ApoE-deficient mice. *J Pharmacol Exp Ther*. 2005;315(1):320-328.

37. Krenek P, Salomone S, Kyselovic J, Wibo M, Morel N, Godfraind T. Lacidipine prevents endothelial dysfunction in salt-loaded stroke-prone hypertensive rats. *Hypertension*. 2001;37(4):1124-1128.

38. Massart PE, Donckier J, Kyselovic J, Godfraind T, Heyndrickx GR, Wibo M. Carvedilol and lacidipine prevent cardiac hypertrophy and endothelin-1 gene overexpression after aortic banding. *Hypertension*. 1999;34(6):1197-1201.

39. Godfraind T, Mennig D, Bravo G, Chalant C, Jaumin P. Inhibition by amlodipine of activity evoked in isolated human coronary arteries by endothelin, prostaglandin F2 alpha and depolarization. *Am J Cardiol*. 1989;64(17):58I-64I.

40. Feron O, Salomone S, Godfraind T. Action of the calcium channel blocker lacidipine on cardiac hypertrophy and endothelin-1 gene expression in stroke-prone hypertensive rats. *Br J Pharmacol*. 1996;118(3):659-664.

41. Feron O, Salomone S, Godfraind T. Blood pressure-independent inhibition by lacidipine of endothelin-1-related cardiac hypertrophy in salt-loaded, stroke-prone spontaneously hypertensive rats. *J Cardiovasc Pharmacol*. 1995;26(suppl 3):S459-S461.

42. Krippeit-Drews P, Morel N, Godfraind T. Effect of nitric oxide on membrane potential and contraction of rat aorta. *J Cardiovasc Pharmacol*. 1992;20(suppl 12):S72-S75.

43. Batova S, DeWever J, Godfraind T, Balligand JL, Dessy C, Feron O. The calcium channel blocker amlodipine promotes the unclamping of eNOS from caveolin in endothelial cells. *Cardiovasc Res*. 2006;71(3):478-485.

44. Salomone S, Silva CL, Morel N, Godfraind T. Facilitation of the vasorelaxant action of calcium antagonists by basal nitric oxide in depolarized artery. *Naunyn Schmiedebergs Arch Pharmacol*. 1996;354(4):505-512.

45. Godfraind T, Salomone S. Calcium antagonists and endothelial function: focus on nitric oxide and endothelin. *Cardiovasc Drugs Ther*. 1996;10(4):439-446.

46. Kyselovic J, Krenek P, Wibo M, Godfraind T. Effects of amlodipine and lacidipine on cardiac remodelling and renin production

in salt-loaded stroke-prone hypertensive rats. *Br J Pharmacol*. 2001;134(7):1516-1522.

47. Balligand JL, Godfraind T. Amlodipine and stroke prevention. *Hypertension*. 2007;50(4):e71.

48. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation*. 1995;92(5):1326-1331.

49. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol*. 2002; 39(2):315-322.

50. Opie LH, Messerli FH. Nifedipine and mortality. Grave defects in the dossier. *Circulation*. 1995;92(5):1068-1073.

51. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002; 288(23):2981-2997.

52. Chrysant SG. The ALLHAT study: results and clinical implications. *QJM*. 2003;96(10):771-773.

53. Group TAOaCftACR. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.

54. Leenen FH, Nwachuku CE, Black HR, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2006;48(3):374-384.

55. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364(9437):849-857.

56. James PA, Oparil S, Carter BL, et al. 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). *JAMA*. 2014;311(5):507-520.

57. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42(6): 1206-1252.

58. Go AS, Bauman M, King SM, et al. An effective approach to high blood pressure control: a science advisory from the American heart association, the American college of cardiology, and the centers for disease control and prevention. *Hypertension*. 2014; 63(12):1230-1238.

59. McDonagh MS, Eden KB, Peterson K. Drug class review on calcium channel blockers. *Drug Class Reviews*. Mar 2005.

60. Ryuzaki M, Nakamoto H, Nishida E, et al. Crossover study of amlodipine versus nifedipine CR with home blood pressure monitoring via cellular phone: internet-mediated open-label crossover trial of calcium channel blockers for hypertension (i-TECHO trial). *J Hypertens*. 2007;25(11):2352-2358.

61. Godfraind T, Egleme C, Finet M, Jaumin P. The actions of nifedipine and nisoldipine on the contractile activity of human coronary

arteries and human cardiac tissue in vitro. *Pharmacol Toxicol.* 1987;61(2):79-84.

62. Pfisterer ME, Zellweger MJ, Gersh BJ. Management of stable coronary artery disease. *Lancet.* 2010;375(9716):763-772.

63. Opie LH. First line drugs in chronic stable effort angina–the case for newer, longer-acting calcium channel blocking agents. *J Am Coll Cardiol.* 2000;36(6):1967-1971.

64. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/ AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American college of cardiology foundation/American heart association task force on practice guidelines, and the American college of physicians, American association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. *Circulation.* 2012; 126(25):e354-e471.

65. Frishman WH.beta-Adrenergic blockade in cardiovascular disease. *J Cardiovasc Pharmacol Ther.* 2013;18(4):310-319.

66. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo-scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005;366(9489):895-906.

67. Zanchetti A, Bond MG, Hennig M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European lacidipine study on atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation.* 2002;106(19):2422-2427.

68. Schamroth L. Immediate effects of intravenous verapamil on atrial fibrillation. *Cardiovasc Res.* 1971;5(4):419-424.

69. Singh BN. A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. *Cardiovasc Res.* 1972;6(2):109-119.

70. Nademanee K, Singh BN. Control of cardiac arrhythmias by calcium antagonism. *Ann N Y Acad Sci.* 1988;522:536-552.

71. Schamroth L, Antman E. Calcium channel blocking agents in the treatment of cardiac arrhythmias, p 347-375. In: Stone PH, and man EM, Eds. *Calcium Channel Blocking Agents in the Treatment of Cardiovascular Disorders.* Mount Cisco, New York: Futura Publishing Company, Inc.; 1983.

72. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European society of cardiology (ESC). *Eur Heart J.* 2010;31(19):2369-2429.

73. De Simone A, De Pasquale M, De Matteis C, et al. VErapamil plus antiarrhythmic drugs reduce atrial fibrillation recurrences after an electrical cardioversion (VEPARAF Study). *Eur Heart J.* 2003;24(15):1425-1429.

74. Bühler F, Bolli W, Müller F, Erne P. Calcium antagonists for identification of mechanisms and treatment of patients with essential hypertension. In: Fleckenstein A, Van Breemen C, Gross R, Hoffmeister F, eds. *Cardiovascular Effects of Dihydropyridine-*

Type Calcium Antagonists and Agonists. Berlin, Heidelberg, New york: Springer; 1985:445-457.

75. Morel N, Godfraind T. Selective interaction of the calcium antagonist amlodipine with calcium channels in arteries of spontaneously hypertensive rats. *J Cardiovasc Pharmacol.* 1994; 24(4):524-533.

76. Zanchetti A, Stella A. The role of the kidney in neurohormonal cardiovascular regulation. *Acta Physiol Scand Suppl.* 1988;571: 69-81.

77. Zanchetti A. The renin-angiotensin system and the heart. *Am J Med.* 1988;84(3A):1-2.

78. Devereux RB, Palmieri V, Sharpe N, et al. Effects of once-daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (preserve) trial. *Circulation.* 2001; 104(11):1248-1254.

79. Godfraind T. Calcium-channel modulators for cardiovascular disease. *Expert Opin Emerg Drugs.* 2006;11(1):49-73.

80. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158.

81. Wang JG, Li Y, Franklin SS, Safar M. Prevention of stroke and myocardial infarction by Amlodipine and Angiotensin receptor blockers. A quantitative overview. *Hypertension.* 2007;50(1):181-188.

82. Sasaki H, Saiki A, Endo K, et al. Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. *J Atheroscler Thromb.* 2009; 16(5):568-575.

83. Ozawa Y, Hayashi K, Nagahama T, Fujiwara K, Wakino S, Saruta T. Renal afferent and efferent arteriolar dilation by nilvadipine: studies in the isolated perfused hydronephrotic kidney. *J Cardiovasc Pharmacol.* 1999;33(2):243-247.

84. Hayashi K, Kumagai H, Saruta T. Effect of efonidipine and ACE inhibitors on proteinuria in human hypertension with renal impairment. *Am J Hypertens.* 2003;16(2):116-122.

85. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, Hecker H, Jost S, Deckers JW. Retardation of angiographic progression of coronary artery disease by nifedipine. Results of the international Nifedipine trial on antiatherosclerotic therapy (INTACT). INTACT group investigators. *Lancet.* 1990;335(8698):1109-1113.

86. Zanchetti A, Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A. The verapamil in hypertension and atherosclerosis study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J Hypertens.* 1998;16(11):1667-1676.

87. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. *Circulation.* 2000;102(13): 1503-1510.

88. Simon A, Gariepy J, Moyse D, Levenson J. Differential effects of nifedipine and co-amilozide on the progression of early carotid wall changes. *Circulation*. 2001;103(24):2949-2954.

89. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the multicenter isradipine diuretic atherosclerosis study (MIDAS). A randomized controlled trial. *JAMA*. 1996; 276(10):785-791.

90. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120(8):713-719.

91. Chrysant SG, Lee J, Melino M, Karki S, Heyrman R. Efficacy and tolerability of amlodipine plus olmesartan medoxomil in patients with difficult-to-treat hypertension. *J Hum Hypertens*. 2010;24(11):730-738.

92. Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30(4):587-604.

93. Oparil S, Chrysant SG, Melino M, Lee J, Karki S, Heyrman R. Long-term efficacy of a combination of amlodipine and olmesartan medoxomil +/- hydrochlorothiazide in patients with hypertension stratified by age, race and diabetes status: a substudy of the COACH trial. *J Hum Hypertens*. 2010;24(12):831-838.

94. Fogari R, Malamani G, Corradi L, et al. Effect of valsartan or olmesartan addition to amlodipine on ankle edema in hypertensive patients. *Adv Ther*. 2010;27(1):48-55.

95. Calhoun DA, Lacourciere Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. 2009;54(1):32-39.

96. Oparil S, Melino M, Lee J, Fernandez V, Heyrman R. Triple therapy with olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide in adult patients with hypertension: The TRINITY multicenter, randomized, double-blind, 12-week, parallel-group study. *Clin Ther*. 2010;32(7):1252-1269.

97. Fogari R, Mugellini A, Preti P, Zoppi A, Derosa G. Valsartan addition to amlodipine is more effective than losartan addition in hypertensive patients inadequately controlled by amlodipine. *Vasc Health Risk Manag*. 2010;6:87-93.

98. Elliott WJ, Calhoun DA, DeLucca PT, Gazdick LP, Kerns DE, Zeldin RK. Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial. *Clin Ther*. 2001;23(8):1166-1179.

99. Stanton T, Reid JL. Fixed dose combination therapy in the treatment of hypertension. *J Hum Hypertens*. 2002;16(2):75-78.

100. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417-2428.

101. Afanas'ev Iu I, Storozhenko S, Grigorova S. [Potentialities of medicinal correction of cerebrovascular disturbances in patients with arterial hypertension]. *Klin Med (Mosk)*. 2012; 90(6):66-69.

102. Efimova I, Kalashnikova TP, Lishmanov Iu B. [The impact of antihypertensive therapy on cerebral hemodynamics in patients with metabolic syndrome]. *Klin Med (Mosk)*. 2012;90(8):36-41.

103. Chalmers J, Arima H, Woodward M, et al. Effects of combination of perindopril, indapamide, and calcium channel blockers in patients with type 2 diabetes mellitus: results from the Action In Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial. *Hypertension*. 2014; 63(2):259-264.

104. Kim-Mitsuyama S, Ogawa H, Matsui K, Jinnouchi T, Jinnouchi H, Arakawa K. An angiotensin II receptor blocker-calcium channel blocker combination prevents cardiovascular events in elderly high-risk hypertensive patients with chronic kidney disease better than high-dose angiotensin II receptor blockade alone. *Kidney Int*. 2013;83(1):167-176.

105. Godfraind T. *Calcium channel blockers*. Basel, Boston: Birkhäuser Verlag; 2004.

106. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122(3):290-300.

107. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326(7404):1427.

108. Bautista LE. Blood pressure-lowering effects of statins: who benefits? *J Hypertens*. 2009;27(7):1478-1484.

109. Martin-Ventura JL, Munoz-Garcia B, Blanco-Colio LM, et al. Treatment with amlodipine and atorvastatin has additive effect on blood and plaque inflammation in hypertensive patients with carotid atherosclerosis. *Kidney Int Suppl*. 2008(111):S71-S74.

110. Neutel JM, Bestermann WH, Dyess EM, et al. The use of a single-pill calcium channel blocker/statin combination in the management of hypertension and dyslipidemia: a randomized, placebo-controlled, multicenter study. *J Clin Hypertens (Greenwich)*. 2009;11(1):22-30.

111. Elliott HL, Meredith PA. Preferential benefits of nifedipine GITS in systolic hypertension and in combination with RAS blockade: further analysis of the 'ACTION' database in patients with angina. *J Hum Hypertens*. 2011;25(1):63-70.

112. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42(9):2672-2713.

113. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. the systolic hypertension in Europe (Syst-Eur) trial investigators. *Lancet*. 1997;350(9080): 757-764.

114. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med*. 2002;162(18):2046-2052.

115. Nimmrich V, Eckert A. Calcium channel blockers and dementia. *Br J Pharmacol*. 2013;169(6):1203-1210.