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REVIEW

Clinical roles of calcium channel blockers in ischemic heart diseases

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Calcium (Ca) channel blockers (CCBs) inhibit Ca^{2+} channels in the myocardium or vascular smooth muscle cells, inhibit myocardium contraction, inhibit the impulse conduction system (anti-arrhythmias) and cause vasodilation. New classifications based on subtypes of Ca channels and α1 subunits have been proposed. Moreover, CCBs have pleiotropic effects on coronary spastic angina (CSA), including variant angina, myocardial infarction (MI) and stent thrombosis (ST). Although the roles of CCBs in clinical situations remain unknown, further studies in this field are expected to broaden our understanding. In this article, we explain the clinical roles of CCBs in ischemic heart diseases, such as CSA, MI and ST, based on previous knowledge and as demonstrated in representative clinical trials.
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INTRODUCTION

Calcium (Ca) channel blockers (CCBs) were first reported in 1969, when Fleckenstein *et al.*[1] in Germany described prenylamine, verapamil and D600 (methoxyverapamil) as coronary vasodilators. Fleckenstein named these agents Ca antagonists, not CCBs, on the basis of their pharmacological effects involving vascular and myocardial stretch activation. These drugs also exert powerful actions on coronary vessels and other smooth muscles, relaxing vascular smooth muscle, uterine smooth muscle and intestinal smooth muscle. The concept of the CCB arose from the advent of the 1,4-dihydropyridine derivative nifedipine (Adalat), which was developed by Vater *et al.*[2] in Germany in 1972, and from basic and clinical studies performed by Fleckenstein *et al.*[3] in Germany and by Hashimoto *et al.*[4] in Japan. Nifedipine is effective for the treatment of ischemic heart disease because it increases coronary blood flow[5] and also has a hypotensive effect.[6] Diltiazem (Herbesser) was developed in Japan,[7] and its effectiveness in variant angina has been demonstrated.[8] Many pharmaceutical companies have shown interest in CCBs; hence, many CCBs have been developed.

CCBs are drugs that target voltage-dependent Ca channels, and new classifications based on subtypes of Ca channels and α1 subunits have been proposed.[9] In this article, we explain the clinical roles of CCBs in coronary spastic angina (CSA), myocardial infarction (MI) and stent thrombosis (ST) on the basis of previous knowledge and as demonstrated in representative clinical trials.

GENERAL BACKGROUND

CCBs bind to voltage-dependent Ca channels in the cell membrane and inhibit the influx of Ca ions into cells. The voltage-dependent Ca channel family members show differences in the potential threshold of depolarization and are classified as high-voltage-activated or low-voltage-activated forms based on their membrane potential dependence. The high-voltage-activated forms include the slow L (long-lasting) type with inert speed, N (neural) types, which are present in regions such as the nerve terminals and P/Q types, which are classified as subtypes of the R type. The low-voltage-activated form includes only the T (transient) type, which has a fast transient inactivation rate, is mainly L-shaped in the myocardium and vascular smooth muscle, and is associated with the T-type pacemaker activity of the sinoatrial node and nerve cells. The Ca channel consists of five subunits (α1, α2, β, γ and δ), each encoded by a separate gene[9] The α1 subunit is the most important; it forms the Ca^{2+} permeation pore and contains a membrane potential detection sensor and the phosphorylation site, which is modified during intracellular signal transduction.

CCBs are classified into the dihydropyridine (DHP) type, the phenylalkylamine (PAA) type or the benzodiazepine (BTZ) type. They have also been classified into three generations based on the timing of their discovery and duration of their action. The first-generation CCBs have a short duration of action and lead to a tachycardia reflex, which is problematic. In the second generation, a sustained-release formulation was developed with long-lasting, stable activity and long-acting antihypertensive effects. The third-generation CCBs, such as amlodipine (Amlodine) and azelnidipine (Calblock), have a long duration of action, produce a small tachycardia reflex, and have high vascular selectivity. The DHP-type CCBs have a high affinity for Ca channels in vascular smooth muscle cells with low membrane potential and have higher activity in vessels than in cardiac muscle cells. They act strongly on vascular smooth muscle, exerting a strong hypotensive effect through peripheral vasodilatation. By contrast, the PAA type CCBs, such as verapamil (Vasolan), act on the impulse conduction system (ICS) with high membrane potential and on

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Table 1 Classification of calcium channel blockers

Classifications		*Drugs*	*Representative drugs*	*Action time*	*Ca^{2+} channel*	*Metabolism*	*Main effect*
Dihydropyridine derivative							Negative inotropic effect
	1st generation	Nifedipine	Adalat	Short	L	CYP3A4	CSA↓
		Nicardipine	Perdipine	Short	L	CYP3A4	Vasodilation
	2nd generation(a)	Nifedipine	Adalat L	Long	L	CYP3A4	
		Nicardipine	Perdipine LA	Long	L	CYP3A4	
	2nd generation(b)	Nilvadipine	Nivadil	Mid	L	CYP3A4	
		Nisoldipine	Baymycard	Mid	L	CYP3A4	
		Nitrendipine		Mid	L	CYP3A4	
		Manidipine	Calslot	Mid	L	CYP3A4	
		Benidipine	Conil	Short	L	CYP3A4	
		Barnidipine		Mid	L	CYP3A4	
		Efonidipine	Landel	Short	L,T	CYP3A4	
		Felodipine		Short	L	CYP3A4	
		Cilnidipine	Atelec	Short	L,N	CYP3A4	
		Aranidipine		Short	L	CYP3A4	
	3rd generation	Amlodipine	Norvasc	Long	L,N	CYP3A4	
		Azelnidipine	Calblock	Long	L	CYP3A4	
Benzodiazepine derivative							Negative inotropic effect
	1st generation	Diltiazem	Herbesser	Mid	L	CYP3A4	CSA↓
	2nd generation(a)	Diltiazem	Herbesser R	Mid	L	CYP3A4	Vasodilation
							ICS↓
Phenylalkylamine derivative							Negative inotropic effect
	1st generation	Verapamil	Vasolan	Short	L	CYP3A4	ICS↓
						CYP3A4 inhibition	
Diarylaminopropylamine derivative							Negative inotropic effect
	3rd generation	Bepridil	Bepricor	Long	L,N	CYP2D6	ICS↓
					Na^+,K^+	CYP2D6 inhibition	Refractory period↑
					Channel		

Abbreviations: CSA, coronary spastic angina; ICS, impulse conduction system.

Ca channels in ventricular muscle, and have negative inotropic, chronotropic and dromotropic effects. The BTZ type, diltiazem, exerts an intermediate effect between the DHP type and PAA type, acting on the myocardium and ICS, particularly in atrioventricular node conduction. Most recently, the diarylaminopropylamine drug bepridil (Bepricor) has been developed (Table 1).[10]

CCBs have pleiotropic effects, such as anti-inflammatory effects, antioxidant effects, inhibition of the migration and proliferation of vascular smooth muscle cells, enhanced nitric oxide (NO) production,[11] plaque stabilization, inhibition of blood vessel aggregation, vasodilation, decreased cardiac contraction and heart rate, and suppressed atrioventricular conduction. Nifedipine is known to increase the levels of adiponectin[12] and peroxisome proliferator-activated receptor-γ,[13] which increase the expression of transcription factors involved in adipocyte differentiation. Moreover, nifedipine has an antioxidant effect,[14–16] improves NO bioavailability[12,17,18] and inhibits vascular smooth muscle migration.[19–21] In addition, it inhibits monocyte chemotactic protein-1 expression,[22–24] thus resulting in anti-inflammatory activity, and is also known to improve vascular remodeling. Amlodipine has a possible inhibitory effect on the onset and progression of atherosclerosis through NO production,[25] has anti-inflammatory[26,27] and antioxidant effects,[28] inhibits the migration and proliferation of vascular smooth muscle cells, stabilizes plaques[29,30] and inhibits platelet aggregation, as shown by basic science and clinical experiments.

The adverse effects of CCBs include palpitations, headache, hot flashes, edema, gingival growth and constipation. Non-DHP CCBs must not be used in patients with heart failure or marked bradycardia because of their cardioinhibitory actions, and careful consideration is necessary regarding their use in elderly patients with latent cardiac disorders or their concomitant use with digitalis or a β-blocker.[31]

The mechanism of action of CCBs is shown in Figure 1. The cardiovascular pharmacological actions of representative CCBs are shown in Table 2, and are based on the literature.[32,33]

CORONARY SPASTIC ANGINA

CCBs, which inhibit the intracellular Ca^{2+} influx in vascular smooth muscle cells, are highly effective for the prevention of coronary spasms and are a first-line treatment for coronary vasospasm.[34,35] In a comparative study of tens of trials, CCBs, regardless of type and time of action, have been shown to be effective at preventing angina attacks.[36–41] In addition, at normal doses, few adverse effects have been reported, thus suggesting that this treatment is safe. A CCB has been reported to inhibit Rho kinase.[42] The possibility that there is a difference in prognosis improvement among patients receiving different CCBs has been suggested.[43,44] However, the combined administration of several CCBs and nitrate drugs has not yielded objective evidence regarding the therapeutic effect. Furthermore, if CCBs are discontinued after a long period, a worsening of symptoms (rebound phenomenon) has been reported.[45–47] In cases of dose increases or discontinuation, dose changes must occur in stages, and

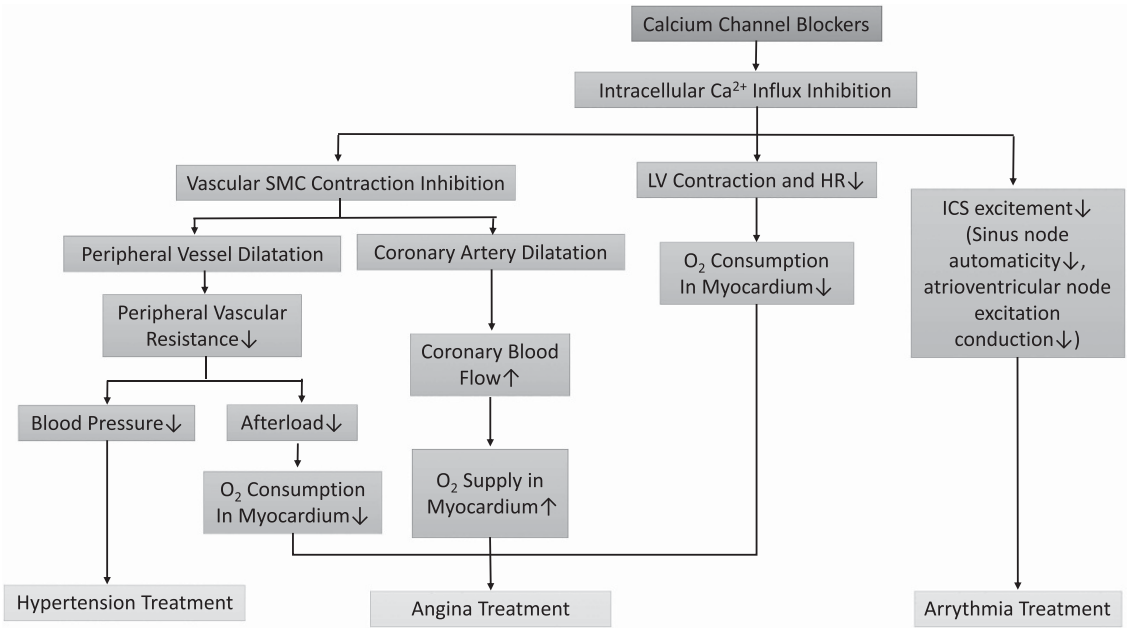

Figure 1 The Mechanism of action of calcium channel blockers. Ca, calcium; SMC, smooth muscle cell; LV, left ventricle; HR, heart rate; ICS, impulse conduction system. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 2 Cardiovascular pharmacological actions of representative calcium channel blockers

	Verapamil	*Diltiazem*	*Nifedipine*
Coronary vasodilation	Strong	Very strong	Very strong
Peripheral vasodilation	Strong	Weak	Very strong
Cardiac contraction	↓↓	↓	↑
Heart rate	↑↓	↓	↑
Atrioventricular conduction	↓↓	↓	↑↓

with each change, it is necessary to confirm that there is no deterioration or coronary spasm by using methods such as Holter monitoring.[38] In some cases of CSA, no attacks occur even after discontinuation of CCBs after a certain period of administration; however, so-called spontaneous remission has been reported.[48,49] Substantial data exist indicating that benidipine (Coniel) significantly improves the prognosis of CSA, particularly the medium- and long-term prognoses.[44] The mechanisms involved in the cardiovascular protective effect include enhanced expression of vascular endothelial NO synthase, amelioration of vascular remodeling and an antioxidant effect, as mentioned above. In Asian countries, including Japan, the incidence of CSA is higher than in Western countries.[50,51] We have recently reported that a variant of aldehyde dehydrogenase 2 is associated with CSA in east Asian patients[52] and that aspirin[53] and statin[54] were promising therapeutic strategies to improve the prognosis of CSA patients.

MYOCARDIAL INFARCTION

The short-acting DHP-type CCB, which was widely used in a high percentage of MI patients until the first half of 1990, was then reported to potentially lead to myocardial ischemia, owing to activation of the sympathetic nerve reflex and the prevalence of tachycardia and hypotension, thereby worsening the prognosis of MI patients, as supported by meta-analysis.[55–57] The contraindication for the administration of this drug to MI patients became dogma in the absence of proof to the contrary.[58–60] However, clinical trials testing the efficacy of the long-acting DHP type of CCBs increasingly confirm the efficacy of this group of drugs alone and in combination with other drugs.[61–64] The Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study in 2008 has examined, through a double-blind design, in 11 506 hypertension patients with high cardiovascular risk, whether the combination of benazepril (Cibacen) and amlodipine is beneficial for preventing cardiovascular events (such as cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for angina, resuscitation from sudden cardiac arrest and coronary revascularization), compared with the combination of benazepril and hydrochlorothiazide (Dichlotride).[65] In the 36-month follow-up period, the total incidence of cardiac events in the amlodipine combination group was significantly lower than in the hydrochlorothiazide combination group, and there was a significant difference in the non-fatal MI recurrence rate when comparing the individual cardiac events.[65] The study did not examine MI secondary prevention directly because MI history patients constituted ~24% of the group; the other participants had angina or coronary risk factors. However, the data demonstrate the superiority of the combination of angiotensin-converting enzyme inhibitors and long-acting DHP-type CCBs for high-risk hypertensive patients, including those with a history of MI.[65]

In patients with MI definitively due to coronary spasm or coronary spastic ischemia attack, prevention by CCBs is presumed to be superior to secondary prevention because such patients are thought to progress to MI as an extension of angina attacks. This type of MI is in contrast to MI due to coronary plaque rupture, which cannot be prevented by suppression of angina attacks. Notably, the relevant patients are those who are clinically diagnosed with CSA or MI derived from coronary spasms. In past reports, coronary spasms have been shown to occur easily by drug provocation testing in the recovery phase after acute MI in Japanese patients.[50,66] At present, it is not certain whether any CCB is effective for patients in whom coronary spasms are easy to provoke. Regarding the effectiveness of heart rate-lowering CCBs (verapamil and diltiazem) as a secondary form of

prevention when β-blockers are contraindicated or poorly tolerated, subanalysis of the INVEST (International Verapamil SR-Trandolapril Study) trial,[67] which examined the utility of verapamil for hypertensive patients with coronary artery disease, has demonstrated that verapamil has equal preventive efficacy to that of atenolol (Tenormin).[68]

STENT THROMBOSIS

ST is a phenomenon in which thrombosis occurs in a deployed stent segment and occludes the coronary artery. When ST occurs, severe outcomes such as acute MI or death are frequent; hence, it is well known as a disease state with poor prognosis. Regarding the time of emergence, ST most commonly occurs within 1 week after stent deployment, often in the late phase. During the drug-eluting stent (DES) era, very late ST was often observed. ST is classified according to the time of emergence. In the past, ST was classified as acute ST (within 24 h after the procedures) or subacute ST (within 30 days after the procedures). However, after the appearance of the DES, very late ST became a clinical issue, and a new definition was adopted. ST is now classified as early ST (within 30 days after the procedures), late ST (from 31 to 365 days after the procedures) or very late ST (>1 year after the procedures).[69,70] Furthermore, as the use of a common international definition to discuss ST became more necessary, the definition from the Academic Research Consortium (ARC) became more widely used.

It is sometimes impossible to determine whether cardiac events or sudden death occurring in the late phase after stent deployment are due to ST. Therefore, ST has been classified according to the degree of reliability of the confirmation. Definitive ST classification requires angiographic[71] or autopsy confirmation of thrombosis or occlusion as an acute coronary syndrome. Probable ST is defined as unaccountable death within 30 days or a lack of confirmed MI in the perfusion area of the target lesion, whereas possible ST is defined as unaccountable death over 30 days after stent deployment.[69,70] ST has emerged as a severe complication of percutaneous coronary intervention.[72] Because the occurrence of ST is lower in Japan than in Western countries,[73,74] there are limited data from which to predict ST after DES implantation in Japan.[75,76] We have examined the independent predictors of ST incidence after DES implantation in Japanese patients, including the use of CCBs, using data from the Kumamoto Intervention Conference Study registry.[77–80] In this registry, CCB use was found to be associated with a decreased risk of ST after DES implantation within 1 year in Japanese patients.[81] The underlying mechanism of the decreased risk of ST in CCB users is thought to be related to the prevalence of coronary spasms. Although the relation between coronary spasms and ST is unclear, given the decreased risk of ST with CCB use, it is possible that coronary spasms may be associated with the pathogenesis of ST as well as the pathophysiology of ischemic heart diseases.

MAJOR CLINICAL TRIALS

Although in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) II study in 2000 (Annual Scientific Session of American College of Cardiology), amlodipine did not seem to have the ability to prevent heart failure or exert therapeutic effects, the A Coronary Disease Trial Investigating Outcome with Nifedipine (ACTION) study in 2004[61] showed that sustained-release nifedipine significantly suppresses the onset of ischemic heart failure, demonstrating that CCBs can offer proactive adaptation in cases of ischemic heart disease.

The status of CCBs as the most reliable type of hypotensive agent is already established. Based on the maintenance of a stricter hypotensive effect and organ protection, the clinical significance of combination therapy has been demonstrated. In The Anglo-Scandinavian Cardiac Outcomes Trial-Conduit Artery Function Evaluation (ASCOT-CAFÉ) trial,[82] the combination of amlodipine and perindopril (Coversyl) was found to ameliorate aortic pulse pressure, which is not detected in peripheral blood pressure, thus highlighting a novel organ protective effect for CCBs.[83] The combination of a CCB and a renin–angiotensin system (RAS) blocker is a focus in recent literature.[84,85] In the nifedipine and candesartan combination (NICE-Combi) trial,[86] low-dose combination therapy with controlled-released nifedipine and candesartan (Blopress) was shown to be superior to up-titrated monotherapy with candesartan in terms of blood pressure control and renal protection in patients with essential hypertension. The ACCOMPLISH trial,[65] comparing benazepril combined with an amlodipine or a hydrochlorothiazide in the prevention of cardiovascular events in high-risk hypertensive patients, demonstrated that the combination of a RAS blocker with a CCB is superior to the combination of a RAS blocker with a diuretic in preventing cardiovascular events in high-risk hypertensive patients. Furthermore, subgroup analysis of the ACCOMPLISH trial showed that the combination of a RAS blocker with a CCB is also superior to the combination of a RAS blocker with a diuretic in diabetic hypertensive patients[87] and that the combination suppresses the risk of renal failure progression.[88] In the OlmeSartan and Calcium Antagonists Randomized (OSCAR) trial,[89] the combination of olmesartan (Benicar, Olmetec) and CCB was found to lower blood pressure and to reduce the incidence of primary end points more effectively than high-dose olmesartan in patients with cardiovascular disease. The addition of a second antihypertensive agent is more effective at lowering blood pressure than simply doubling the dose of an existing agent.

SUMMARY

CCBs inhibit Ca^{2+} channels in the myocardium or vascular smooth muscle cells, resulting in inhibition of myocardium contraction, inhibition of ICS (anti-arrhythmias) and vasodilation. Moreover, CCBs have a pleiotropic effect on CSA including variant angina, MI and ST. Furthermore, new mechanisms of action of Ca^{2+} channels, such as the aldosterone inhibition effect and mineralocorticoid receptor blockade effect, have been elucidated in the field of endocrinology.[90–92] Although the roles of CCBs in clinical situations remain unknown, further studies in this field are expected to broaden our understanding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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