L- and T-type calcium channel blockade - the
efficacy of the calcium channel antagonist
mibefradil

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Calcium channel antagonists (CCA) are potent vasodilators widely used in the treatment of hypertension and angina pectoris. CCA have also been proposed for the prevention of cardiac events after myocardial infarction. Despite different chemical structures, most of the available CCA used today act via inhibition of the slow Ca\(^{2+}\)-inward current through L-type calcium channels. Three main classes of CCA have been described: 1. dihydropyridines (eg, nifedipine), 2. phenylalkylamines (eg, verapamil) and 3. benzothiazepines (eg, diltiazem). Unwanted effects of some CCA (eg, atrioventricular blockade (AV), negative inotropic action, neurohormonal activation) often limit their therapeutic use.

In addition, most CCA have a rather poor bioavailability due to a large first-pass effect and a short half-life (except the novel dihydropyridine compound, amlodipine) requiring slow-release formulation for once-a-day dosing.

Mibefradil is a tetrazolium CCA featuring an inhibition of both L- and T-type calcium channels with a higher selectivity for T-type than L-type calcium channels. The chemical structure of the compound has been derived from verapamil. Mibefradil has potent blood pressure reducing actions in hypertensive patients, and appears to have preferential coronary vasodilative effects as well as lack of negative inotropic actions at therapeutic dosage. Thus, mibefradil offers a new concept in calcium channel antagonism, and can be regarded as a pharmacologically important new development within the group of CCA.

**Indications and limitations of calcium channel antagonists (CCA)**

CCA are distinguished by their heterogeneous composition. They were arranged following the WHO-classification of 1987 [1] in compounds with a selective inhibition of the L-type voltage-gated plasma membrane calcium channel with high affinity concentration and compounds with low specificity and affinity to the L-type calcium channel. The compounds with high affinity and specificity to these calcium channels were divided in three main classes according to their different chemical structures: 1. dihydropyridines (eg, nifedipine), 2. phenylalkylamines (eg, verapamil) and 3. benzothiazepines (eg, diltiazem). CCA with low affinity and specificity for the L-type calcium channels are, for instance, flunaricid, prenylamine and lidoflacine [2].

The differences between their pharmacological properties determine the clinical use of these compounds. The dihydropyridines are used predominantly in the treatment of arterial hypertension and coronary heart disease [3]; the phenylalkylamines in supraventricular tachycardia, angina pectoris and arterial hypertension; the benzothiazepines in coronary heart disease, arterial hypertension and supraventricular tachycardia. The pharmacological profile and the mode of action of the CCA currently used for the treatment of cardiovascular diseases are well established [4, 5]. In addition to their main indications mentioned above, CCA have also been used in the therapy of stable and vasospastic angina pectoris, late intervention after myocardial infarction as well as in subarachnoidal haemorrhage, Raynaud’s syndrome and hypertrophic obstructive cardiomyopathy.

The relative clinical importance of the L-type CCA in the therapy of hypertension and coronary heart disease depends on their very different characteristics concerning efficacy and tolerability. Their therapeutic use is often limited by the appearance of unwanted side effects. For instance, dihydropyridines can induce ankle oedema, headache, and flush [6]. In addition, these compounds can initiate reflex tachycardia in response to peripheral vasodilatation and can exert proischaemic effects [7]. Verapamil and diltiazem can exert negative chronotropic and dromotrop actions with prolonged atrioventricular conduction. Furthermore, L-type CCA can reduce the contractility of the heart muscle [8]. The potential for negative inotropic actions of the L-type CCA, inherent to their mechanism of action, and their propensity for neurohormonal activation [9] can entail dangerous consequences in patients with limited left ventricular function. The combined therapy of diltiazem/verapamil and β-receptor blockers can engender well known complications like AV-block or considerable bradycardia.

Major differences between the L-type CCA exist with respect to their pharmacokinetic profile. Nifedipine and verapamil are quickly eliminated leading to relatively short blood pressure lowering effects of less than 24 hour duration.

**Key words:** calcium channel antagonists, L-type calcium channel, T-type calcium channel, mibefradil
Verapamil (and diltiazem) influence the intestinal transit time which can cause constipation. Further limiting pharmacokinetic features of different CCA are low bioavailability, interactions with food [10] and dependence of elimination on renal function [11].

These disadvantageous properties have limited the therapeutic use of first generation L-type CCA and necessitated further efforts in drug development. The first strategy was to improve the galenic of the prototypes (retarded verapamil [12] and nifedipine, GITs-form of nifedipine) or to create compounds with more pronounced calcium channel inhibiting action or increased tissue specificity. The following generations of L-type CCA featured more constant plasma levels with less occurrence of unwanted side effects and the potential for once-a-day dosing (eg, amloidipine, lacidipine). Other, more recent, CCA were distinguished by a higher tissue specificity, eg, the dihydropyridine derivate nimodipine, which reportedly features a higher selectivity for the cerebral vasculature [13, 14].

In general, new CCA should combine the following desired properties: a) high bioavailability, b) long half-life, allowing once-a-day dosing, c) lack of negative inotropism, d) absence of reflex stimulation of the neurohormonal axis, e) antidiabetic efficacy.

The structure of the calcium channels

Calcium channels are classified according to their functional (physiological properties) and structural (molecular biological properties) characteristics and their selective occurrence on different cell types. They have been divided in six major groups and designated N-, P-, Q-, R-, L- and T-type calcium channels according to the functional classification and location on different tissues [15].

The calcium channels are large transmembrane peptide molecules which participate in the Ca\textsuperscript{2+} influx into cells through the cell membrane or in Ca\textsuperscript{2+} release from intracellular stores such as the endoplasmatic reticulum. Calcium channels play an important role in the excitation-contraction coupling mechanism in skeletal-, vascular- and cardiac muscle cells and in the control of neurotransmitter release in the central and peripheral nervous system. Voltage-dependent calcium channels permit the Ca\textsuperscript{2+} entry in response to membrane depolarization. Receptor-operated calcium channels are influenced, for instance, by \(\alpha\)-adrenoreceptor agonists such as adrenaline and noradrenaline via the intracellular inositol-triphosphate (IP\textsubscript{3}) pathway or by \(\alpha\)- or \(\beta\)-adrenoreceptor agonists via G-protein mediated mechanisms. The increased cytosolic Ca\textsuperscript{2+} level initiates contraction in muscle cells and the release of neurotransmitters in neuronal cells [16].

Calcium channels display a complex structure consisting of five units: \(\alpha_1\), \(\alpha_2\), \(\beta\), \(\gamma\) and \(\delta\) [17]. The \(\alpha_1\) unit is a hydrophobe polypeptide with 4 subunits (I-IV) and is divided into \(\alpha_1A\), \(\alpha_1B\), \(\alpha_1C\), \(\alpha_1D\), \(\alpha_1E\) and \(\alpha_1S\) according to the calcium channel classes [18]. Each subunit of the \(\alpha_1\) unit has six putative membrane-spanning \(\alpha\)-helical segments (S1-6). Each third and fourth amino acid of the S4-segments contains a positive arginine or lysine which most likely represents the third and fourth amino acid of the S4-segments contains a hydrophobe polypeptide with 4 subunits (I-IV) and is divided in six major groups and designated N-, P-, Q-, R-, L- and T-type calcium channels according to the functional classification and location on different tissues [15].

The \(\alpha_2\) unit is an extracellular, highly glycosylated protein and is supposed to enhance the Ca\textsuperscript{2+} influx through the P-region [25].

The \(\beta\) unit is a small intracellular protein which interacts with the I-II linker of the \(\alpha_1\) unit and seems to exert an enhancing action on the conductance ability of the calcium channel [18]. The \(\beta\) unit has been classified into four major classes, namely \(\beta_1\), \(\beta_2\), \(\beta_3\) and \(\beta_4\) [26].

The \(\gamma\) unit is a 223 amino acid protein isolated from skeletal muscle of the rat sharing 84 \% and 79 \% identity with the human and rabbit skeletal muscle \(\gamma\) unit respectively [27]. In several experiments, it could be demonstrated that transient coexpression of the skeletal muscle \(\gamma\) unit with the cardiac calcium channel complex shifts the inactivation curve to negative potentials and accelerates current inactivation without changing other voltage-dependent properties of the calcium channel.

The \(\delta\) unit is associated with the \(\alpha_2\) unit and is the connecting element to the \(\alpha_2\) unit. It is supposed that the \(\omega-\delta\) association modulates ligand binding either by a direct contribution to the dihydropyridine binding site or by altering the drug binding site on the \(\alpha_1\) unit [28, 29]. In addition, the coexpression of the \(\alpha_2\)8 unit with the \(\alpha_1\) and \(\beta\) units in HEK 293 cells increases the number of functional L-type calcium channels at the cell surface [30].

Physiological properties of the L- and T-type calcium channels

Two different types of voltage-gated calcium channels are classified according to their dependence on the degree of depolarization and their duration of opening: high voltage-activated (HVA) calcium channels like the L-, P-, Q-, R- and N-type calcium channels and low voltage-activated (LVA) calcium channels like the T-type calcium channel.

Figure 1. Schematic representation of the \(\alpha_1\) unit of the calcium channel with its structural composition of subunits I-IV and segments S1-S6, and the functional importance of the several components.
The L-type calcium channels are located in all excitable and in many non excitable tissues. L-type calcium channels regulate muscle contractility in cardiac, skeletal and smooth muscle cells because they represent the most important transport mechanism of Ca\(^{2+}\) through the cell membrane of these cells. They also participate in transmitter release from endocrine and neuronal tissues. The activation potential of these channels is around -10 mV and the single channel conductance is high \(\approx 100\) picosiemens, measured for \(100\) mM Ba\(^{2+}\) as the charge carrier). The time course of inactivation of this channel type is relatively long which gave rise to their name “L-type” calcium channel (long lasting). Opening and closing of L-type calcium channels is 10- to 100-times slower in skeletal muscle cells than in cardiac muscle cells [31]. The neuronal L-type calcium channels can be inhibited by naturally existing animal poisons (eg, mamba snake, cone snail) like calcicludine and calciacpite. All known therapeutically used CCA inhibit the L-type calcium channels.

The T-type calcium channels are located in excitable and non excitable cells. Relatively high density is found in smooth muscle cells of arteries, in the adrenal gland and in cardiac cells with pacemaker activity such as the atrial sinus node. In cardiac cells, they are thought to support the pacemaker action and to participate in the Ca\(^{2+}\) influx into myocytes after small potential changes. Their activation potential is very low in the range of -70 mV. The single channel conductance of the T-type calcium channels is small \(8\) picosiemens, measured for \(100\) mM Ba\(^{2+}\) as the charge carrier) and their time course of inactivation is fast. Thus, the opening and closing time of the T-type calcium channels is very short resulting in a transient Ca\(^{2+}\) influx. For this reason, this type of calcium channel has been termed “T-type” channel (transient). The T-type calcium channels are inhibited by Ni\(^{2+}\), amiloride, tetramethrin, ethosuximide and the CCA, mibefradil.

**Potential importance of the T-type calcium channels**

T-type calcium channels open following small changes of the resting membrane potential in the order of magnitude of spontaneous depolarization, suggesting that these channels participate in spontaneous autonomous excitation and in pacemaker activity [32]. This hypothesis is supported by the presence of T-type calcium channels in cardiac cells with spontaneous activity (eg, the atrial sinus node) [33]. T-type calcium channels were also found in rapidly proliferating fibroblasts [34, 35] and smooth muscle cells [36, 37] as well as in adrenal cells and neuronal cells [38]. This channel type has also been shown to mediate the sustained increase of intracellular Ca\(^{2+}\) induced by angiotensin II [39], endothelin [40] and PDGF [41]. In addition, some studies have shown that T-type calcium channels abundantly exist in embryonic tissues and that changes of their density correlated with growth rate [42]. In contrast, the density of L-type calcium channels was shown to be constant in all phases of development. These findings indicate that T-type calcium channels are involved in cell growth and proliferation and that these channels participate in processes of development.

Investigations in cardiac tissues demonstrated that T-type calcium channels are overexpressed in hypertrophied myocardial cells of failing hearts [43] but not in healthy adult rat hearts [44, 45]. In support of these facts, studies on cardiac ventricular myocytes from hamsters with cardiomyopathy have shown that the T-type calcium channel density, but not the L-type calcium channel density, was increased after these cells had undergone hypertrophy or proliferation [46]. Experiments with hypertrophied adult feline left ventricular myocardium have shown an increased activity of T-type calcium channels associated with the development of an active growth phase stimulated by pressure overload [43]. The participation of T-type calcium channels in pathological remodeling of myocytes was delineated from these studies.

**Action of mibefradil on L- and T-type calcium channels**

The binding sites of the three main classes of CCA (dihydropyridines, phenylalkylamines, benzothiazepines) have been intensively investigated. In addition, two separate interaction sites were identified for diphenylbutylpiperidines (fluspirilene) and indolizinesulfones (fantofarone) [47]. These CCA all interact with the \(\alpha_1\) unit of the L-type calcium channel in an allosteric manner but each group of compounds has its own binding site. The interaction domain of dihydropyridines was identified in the S6 segment and in the extracellular SS-S6 linker of the subunits III and IV of the \(\alpha_1\) unit [48–50], as well as two amino acid residues of the SS segment of the subunit III [51]. The receptor domain for diltiazem was located within or in close proximity to the segment 6 of the subunits III and IV, but was not identical with those for gallopamil or verapamil [52, 53]. A single binding site of mibefradil of the \(\alpha_1\) unit of the L-type calcium channel has been identified which differs with respect to the effects of auxiliary units \(\alpha_2, \beta \), and \(\delta\) unit of the L-type calcium channel) and G-protein units as compared to the verapamil binding site [54]. The interaction site of mibefradil overlaps with the desmethoxyverapamil–, diltiazem– and fantofofarone- but not with the dihydropyridine binding sites, and a limited interaction with the fluspirilene binding site has been observed [55, 56] (figure 2). In addition, concentrations of up to 10 \(\mu M\) mibefradil did not inhibit the binding site of dihydropyridines [56] whereas verapamil does [57].

Voltage clamp experiments performed with isolated guinea pig myocytes have shown that mibefradil blocked the Ca\(^{2+}\) current through L-type calcium channels with an IC\(_{50}\) of 0.2 \(\mu M\). In the same experiment, mibefradil blocked the Na\(^+\) current with an IC\(_{50}\) of 55 \(\mu M\) [58]. These results demonstrate the high selectivity of mibefradil for L-type calcium channels over Na\(^+\)-channels.

It has further been shown that mibefradil selectively, but not specifically, inhibits the T-type calcium channels [59]. To determine the inhibitory action of mibefradil on T-type versus L-type calcium channels, measurements of Ca\(^{2+}\) currents using Ba\(^{2+}\) as the charge carrier were performed in rat vascu-
Mibefradil can also exert an inhibitory action on volume-activated Cl- currents in calf pulmonary artery endothelial cells (CPAE) [60]. In these experiments using the patch clamp and the Fura-II microfluorescence technique, it was found that mibefradil efficiently inhibited both Ca2+-activated and volume-activated Cl- currents (figure 5). These effects of mibefradil together with its effects on T-type calcium channel might modulate Ca2+ signalling in endothelial cells and contribute to its complex cardiovascular actions. Interestingly, mibefradil showed in the same experiments an inhibitory action on proliferation of CPAE cells with a half-maximal inhibition by 1.7 ± 0.12 µM, which is approximate to the concentration for half-maximal block of Cl- channels (figure 6).

**Pharmacological profile of mibefradil in preclinical studies**

**Pharmacokinetics**

A lot of preclinical experiments have been performed to investigate the pharmacokinetic profile of mibefradil. The pharmacokinetics of single- and multiple-doses of mibefradil were studied in a chronically instrumented dog model [61]. In these experiments, four female dogs received a single i.v. dose (1 mg/kg), three single p.o. doses (1, 3 and 6 mg/kg) and a regimen of 3 mg/kg p.o. doses twice per day for 8 days. Data on i.v. administration showed that hepatic clearance and systemic clearance values were similar, suggesting that the liver is the main eliminating organ. The fraction of all p.o. administered doses of mibefradil absorbed by the gut was approximately 60 %, indicating that incomplete absorption and/or first-pass gut metabolism occurred. The absolute bioavailability after multiple dosing was increased because of a dose-dependent and duration-of-treatment-dependent reduction in hepatic elimination. This change was mainly caused by a decrease of...
systemic clearance. These data indicate a non-linear pharmacokinetic of mibefradil after p.o. dosing in dogs. Both changes, increase in bioavailability and reduction in systemic clearance, were attributed to a reduction in the ability of the liver to eliminate the drug.

Metabolism
The metabolism of mibefradil has been examined in rat, marmoset, cynomolgus monkey, rabbit and man after single and multiple oral administration [62, 63]. Less than 3 % of an oral dose of mibefradil is recoverable unchanged in urine, and elimination is almost exclusively by metabolism. Mibefradil was converted to some 30 metabolites typically representing between 50 and 80 % of the circulating drug-related material after single oral doses of mibefradil. There are two metabolic pathways responsible for clearance of the drug: hydrolysis of the ester side-chain by a low-affinity, high-capacity esterase to give the major circulating alcohol metabolite RO 40-5966, and cytochrome P_{450}-3A4-mediated oxidation of carbon atoms. The hydrolysis was especially marked in the cynomolgus monkey and rabbit, less in man and least in the rat and marmoset. The extremely low plasma level of mibefradil in the cynomolgus monkey resulted from very efficient first-pass hydrolysis of the side-chain in these animals. Experiments in rats demonstrated that the pharmacodynamic activity of RO 40-5966 is approximately 10 % that of unchanged mibefradil. Cytochrome P450-3A4 oxidative pathways include O-demethylation of the side-chain, N-demethylation and ring-hydroxylation. The oxidative pathways of the alcohol metabolite RO 40-5966 is also mediated via cytochrome P_{450}-3A4 [64].

Mibefradil in experimental models
A number of experimental studies have been performed to determine the pharmacological profile of mibefradil with respect to most effective antihypertensive dosage, vascular selectivity, influence on cardiac contractility, possible stimulation of the renin angiotensin or neurohormonal system and antihypertrophic and antiischaemic action.

Antihypertensive properties
The antihypertensive effects of mibefradil were tested in three rat models of hypertension: spontaneously hypertensive rats (SHR), two-kidney-one-clip renal hypertensive rats, and deoxycorticosterone acetate NaCl rats (DOCA-salt rats) [65]. Mibefradil induced a blood pressure decrease in all three rat models independently of the renin angiotensin or neurohormonal system with three times higher potency than the CCA verapamil. The duration of blood pressure reduction induced by mibefradil
was longer than the one induced by verapamil when doses of comparable initial blood pressure reduction were used [66]. In contrast to diltiazem, the reduction of arterial blood pressure induced by mibebradil was not associated with an increase of heart rate [67]. In these experiments, the plasma noradrenaline level was more increased after diltiazem than mubefradil treatment. The effects of mibebradil on vascular function were investigated in experiments performed with aortic tissue of hypertensive salt sensitive Dahl-rats demonstrating that chronic treatment with mibebradil, like some dihydropyridines, lowered arterial blood pressure and potentiated the endothelium-dependent relaxations by augmented sensitivity of the vascular smooth muscle to endothelium-derived relaxing factor (EDRF, NO) [68], increased the release of EDRF and reduced endothelium-dependent contractions in isolated dog arteries [69].

In summary of these experiments, the antihypertensive properties of mibebradil were derived from a direct action on vascular smooth muscle via inhibition of calcium-dependent contraction as well as an interference with endothelium-dependent responses. The effective reduction of arterial blood pressure was associated with improved endothelial function but without induction of extensive reflex tachycardia or affecting the renin angiotensin system.

**Effect on the intracellular Ca\(^{2+}\) level in vascular smooth muscle and cardiac cells**

The calcium channel antagonistic effect of mibebradil on the intracellular Ca\(^{2+}\) level was studied in vascular smooth muscle cells from the rabbit aorta (VSMC) using the Fura-II measurement method [70]. The results demonstrated that mibebradil in concentration of 1–10 µM completely blocked the angiotensin II stimulated entry of divalent cations into these cells. In the same experiment, mibebradil inhibited the Ca\(^{2+}\) depletion from intracellular stores induced by thapsigargin or 2,5-di-tet-try-butylhydroquinone. As a result of this study, mibebradil prevented an increase of intracellular Ca\(^{2+}\) concentration in VSMC induced by vasoactive hormones. In addition, mibebradil pretreatment of dog coronary arterial vascular muscle cells significantly reduced intracellular Ca\(^{2+}\) activity during stimulation with noradrenaline [71]. Our own unpublished findings show that mibebradil pretreatment prevented an increase of intracellular Ca\(^{2+}\) concentration after MI in the rat left ventricular papillary muscle (Sandmann et al., in preparation). The inhibition of Ca\(^{2+}\) entry into the cell after ischaemic events could stem from the fact that mibebradil blocks Ca\(^{2+}\) entry more potently in depolarized cells, because ischaemic myocardial tissue is depolarized [72]. Measurements of the inward Ca\(^{2+}\) current performed in isolated myocytes using the whole-cell patch-clamp technique demonstrated a concentration- and potential-dependent inhibition of the Ca\(^{2+}\) current by mibebradil into these cells [73]. In contrast to verapamil, mibebradil was more effective at inhibiting the Ca\(^{2+}\) inward current at the membrane resting potential (–80 mV). The potential-dependency of the calcium channel blockade was more pronounced for mibebradil as compared to verapamil indicating that both drugs differ in their kinetics of blockade and recovery from blockade.

**Selectivity to coronary arteries**

In addition to its general vasodilatory and antihypertensive effects, mibebradil has been shown to induce selective vasodilation of coronary arteries with increased coronary blood flow in isolated perfused dog hearts [74] and in hypertensive rats [65, 75]. In these experiments, mibebradil (1 mg/kg i.v.) increased the regional blood flow in coronary arteries in normotensive rats, while there was little change of blood flow in other organs. In addition, mibebradil increased the coronary blood flow in dogs to a greater extent than verapamil (figure 7) [76]. A marked vasodilatory action of mibebradil on the coronary arteries has been demonstrated in isolated, perfused guinea pig hearts showing that mibebradil produced a larger increase in coronary blood flow and, at the same time, a smaller decrease in left ventricular pressure than other CCA [56]. Furthermore, in contrast to mibebradil, the doses of verapamil and diltiazem needed to double coronary blood flow were very close to those producing first-degree AV-block [77]. The dilative action of mibebradil on coronary arteries is thought to be mediated by a direct inhibition of vascular smooth muscle contraction via L- and/or T-type calcium channels as well as an endothelium-dependent relaxation by increasing the release of EDRF [68].

Regarding the selective coronary dilation in rats it is interesting to note that no T-type calcium channels appear to be present in human coronary arteries [78]. In these experiments, a T-type Ca\(^{2+}\) current could be measured using the whole-cell voltage-clamp technique only in primary cultures of human coronary myocytes, but not in coronary myocytes immediately after enzymatic dissociation from heart-transplant patients. These results suggest that L-type calcium channels are the major pathway for voltage-gated Ca\(^{2+}\) entry in human coronary myocytes. The expression of T-type calcium channels in human coronary myocytes in culture may have been triggered by cell proliferation.

The presence of cardiac T-type calcium channels in smooth muscle cells of coronary arteries and in the sinus node could explain the selectivity of mibebradil for the coronary arteries and the cardiac effects of the drug like increasing coronary blood flow by dilation of coronary arteries and decrease of heart rate.

**Reduction of heart rate**

The haemodynamic profile of mibebradil was investigated in conscious normotensive rats and compared to that of diltiazem, verapamil and amiodipine [79]. Despite similar decrease in arterial pressure after intravenous injection of the four drugs, verapamil and diltiazem did not alter heart rate, whereas mibebradil induced a slight decrease of heart rate. In contrast, amiodipine induced a reflex tachycardia. In the same
Blockade of vascular T-type calcium channels

Some experimental studies were performed to investigate the contribution of T-type calcium channels in processes of vascular growth and proliferation as well as in the cardiac hypertrophy and remodeling. Because T-type calcium channels are present in rapidly proliferating cells and mediate the increase of intracellular Ca\(^{2+}\) induced by some growth factors (eg, PDGF, Ang II, endothelin), some investigators have speculated that the proliferation of the vascular muscle cells is related to the activity of the T-type calcium channels. To test this hypothesis, the effects of mibefradil on neointima proliferation after vascular injury in rats were investigated and compared to those of equihypotensive doses of amiodipine and verapamil [81, 82]. 14 days after balloon catheter injury of the carotid artery the area of neointima formation was drastically reduced by mibefradil (54 %) but to a much lesser extent by the L-type CCA amiodipine and verapamil despite to their blood pressure reduction. In the same experiments mibefradil and amiodipine inhibited the smooth muscle cells proliferation. The effects of mibefradil on neointima formation after carotid injury in normotensive and DOCA-salt hypertensive rats were compared to those of the ACE inhibitor cilazapril [83]. The neointima/media ratio of the carotid arteries was significantly reduced and the cardiac metabolic status was improved [88]. The effect of mibefradil on cardiac remodeling processes needs to be investigated. The higher number and activity of T-type calcium channels under hypertrophic conditions in heart failure indicates a contribution of this channel type in hypertrophic and proliferative processes.

Cardiac contractility

The effects of mibefradil on systemic hemodynamics and plasma noradrenaline levels were investigated in experiments using conscious dogs subjected to right ventricular pacing (250 beats/min, 3 weeks). In contrast to diltiazem, mibefradil did not decrease cardiac contractility but increased cardiac output. Plasma noradrenaline levels were three times more increased after diltiazem treatment than after mibefradil treatment [67]. Thus, while diltiazem exerted unwanted actions on cardiac function (negative inotropy, sympathetic stimulation), mibefradil did not seem to worsen cardiac function in this experimental model of heart failure. In addition, the effects of mibefradil on cardiac contractility were investigated in isolated perfused rat hearts and in conscious rats after chronic myocardial infarction and compared to those of diltiazem [89]. In these experiments, in vitro as well as in vivo, mibefradil did not decrease cardiac contractility, whereas diltiazem exerted a strong negative inotropic effect in vivo. In the same model, verapamil and to a lesser extent amiodipine exhibited negative inotropy at equipotent doses [79, 90]. Experiments performed on isolated, electrically stimulated left ventricular papillary muscle strips from failing human hearts demonstrated that nifedipine, verapamil and mibefradil depressed basal contraction force in a concentration-dependent manner [91]. The effect started at concentrations > 0.001 µM demonstrated that chronic administration of 30 mg/kg/d p.o. mibefradil abolished vascular fibrinoid necrosis formation in the brain and reduced arterial thickness in the cerebral artery as well as in the aorta [84]. In summary, mibefradil could exert a vascular protection via inhibition of the T-type Ca\(^{2+}\) current resulting in antiproliferative effect and prevention of pathological structural alterations and remodeling processes in the arterial wall.

Role of cardiac T-type calcium channels

Experiments performed in myocytes of cardiomyopathic hamsters demonstrated that the density of T-type calcium channel currents was increased, and abnormal channel activity and inactivation kinetics were observed, whereas the density of L-type calcium channel currents and activity were constant [46]. The fact that T-type calcium channels are overexpressed in hypertrophied myocardial cells of failing hearts [43] but not in healthy adult rat hearts [44, 45] suggests that the cardioprotective effects of mibefradil might be more pronounced in the failing heart. The effects of mibefradil on cardiac remodeling in renovascular hypertensive rats were compared to those of the ACE inhibitor enalapril. Six weeks after renal artery clipping, equihypotensive doses of both drugs reduced left ventricular hypertrophy. However, enalapril was more effective than mibefradil in regression of cardiac fibrosis resulting in the decrease of interstitial and perivascular collagen content [85]. This effect of enalapril seems to be related to the inhibition of ACE resulting in the reduction of the trophic action of angiotensin II. However, previous studies have demonstrated that cardiac necrosis can also be prevented by verapamil [86, 87]. Studies using a model of permanent coronary occlusion in the rat demonstrated in animals receiving an intravenous infusion of diltiazem 20 min before and during 60 min after ligation, that myocardial necrosis was significantly reduced and the cardiac metabolic status was improved [88]. The effect of mibefradil on cardiac remodeling processes needs to be investigated. The higher number and activity of T-type calcium channels under hypertrophic conditions in heart failure indicates a contribution of this channel type in hypertrophic and proliferative processes.
for nifedipine, > 0.01 µM for verapamil and > 10 µM for mibefradil. A rightward shift of the inotropic concentration-response curves to Ca^{2+} and a depression of the maximal effects of Ca^{2+} were only observed in the presence of nifedipine and verapamil, but not after mibefradil administration (figure 8).

The lack of negative inotropic action of mibefradil could be explained by the selectivity of the drug for T-type calcium channels which are present in vascular smooth muscle cells and in the sinus node, but not in adult healthy ventricular myocytes. Thus, the blockade of T-type calcium channels by mibefradil induced an arterial dilation and a decrease in heart rate without a reduction of cardiac contractility.

**Influence on renal function**

In two-kidney-one-clip renal hypertensive rats similarly blood pressure reducing doses of mibefradil and enalapril worsen the damage of the clipped kidney [92]. In contrast to enalapril, the protection of the non-clipped kidney with respect to the occurrence of the vascular damage was more pronounced by mibefradil. In the same experiment mibefradil was more effective in preventing the hypertension induced increase of plasma creatinine and urea. In stroke-prone spontaneously hypertensive rats the chronic treatment with mibefradil (30 mg/kg/d p.o.) opposed the increase in diuresis and proteinuria [84]. In addition, the decrease of arterial blood pressure by mibefradil in chronically instrumentated, spontaneously hypertensive rats was not accompanied by the decrease of renal blood flow as observed for equihypotensive doses of nifedipine, verapamil and amlodipine. The renal resistance was decreased by mibefradil, nifedipine and amlodipine, whereas no changes were found using verapamil (Chung et al, in preparation). The protection of the renal function by mibefradil could be explained by the selective blockade of T-type calcium channels implying an inhibition of positive chronotropic effects and the lack of neurohormonal stimulation leading to preservation of vasodilatory actions in peripheral vessels. The effects of a long-term treatment with mibefradil (30 mg/kg/p.o.) on the morphology of small arteries were compared to those of a cilazapril treatment (7.5–10 mg/kg in the drinking water) in spontaneously hypertensive rats [93]. 14 weeks after treatment cilazapril increased lumen, decreased media thickness and media-to-lumen ratio in renal as well as in coronary, mesenteric and femoral arteries whereas mibefradil induced a regression of luminal diameter only in mesenteric and femoral small arteries and decreased media thickness and media-to-lumen ratio in all four vascular beds. Thus, cilazapril and mibefradil were effective in regression of hypertension-induced remodeling processes of small arteries despite their different action mechanisms.

**Antiischaemic properties**

The specificity of the beneficial effects of CCA in the ischaemic heart is still a matter of debate. Some experimental stud-
ies were performed to investigate the antiischaemic mechanism of mibebradil in acute and chronic models of heart disease and compared to that of verapamil and amlodipine. In acute reperfusion experiments of myocardial infarction (60 min of regional ischaemia followed by 3h of reperfusion) in dogs, mibebradil (3 mg/kg i.v.) and verapamil (1 mg/kg i.v.) exerted an equal infarct size limiting effect [76]. Similarly in a rat model of ischaemia and reperfusion intravenous administration of mibebradil reduced infarct size to a similar extent as produced by verapamil [94]. We have recently observed that mibebradil exerted marked cardioprotective actions in the experimental model of chronic myocardial infarction-induced cardiac failure in rats. In these experiments 6 weeks of mibebradil treatment (10 mg/kg/d p.o.) reduced infarct size (figure 9) and improved hemodynamic parameters when treatment was begun seven days prior or within 24 hours after induction of myocardial infarction [95]. In an open-chest dog model of short myocardial ischaemia (2-min coronary stenosis), mibebradil and amlodipine showed a similar relationship between the decrease of the rate-pressure product and the antiischaemic effect, but only mibebradil reduced heart rate. Both mibebradil and amlodipine restored the segmental shortening (76% and 68%) in the ischaemic area as compared with preischaemic values [96]. The authors concluded from these results that the antiischaemic effect was heart rate-dependent for mibebradil and mainly afterload-dependent for amlodipine.

The antiischaemic effect of mibebradil seems to be indirectly related to the blockade of T-type calcium channels. The inhibition of this channel type induced a decrease in heart rate because of their localization in the sinus node cells and their participation in pacemaker activity. The reduction in heart rate is associated with reduced oxygen demand of failing hearts. On the other hand mibebradil increased coronary blood flow and thereby myocardial oxygen supply. In addition, results of further studies have shown that mibebradil reduced ischaemia induced sympathetic activation and reflex tachycardia [90, 97-99]. Thus, mibebradil exerted antiischaemic properties via reduction of afterload and heart rate, the increase of coronary blood flow and the absence of reflex tachycardia.

In a rat model of chronic heart failure, the effects of a nine month treatment on survival, hemodynamic variables and cardiac remodeling were compared between mibebradil (15 mg/kg/d) and cilazapril (10 mg/kg/d). In these experiments both drugs decreased left ventricular enddiastolic and central venous pressure without altering of cardiac contractility or heart rate. Furthermore, mibebradil and cilazapril exerted an increase of survival rate (figure 10) and normalized left ventricular collagen density. These results indicate that mibebradil improved survival to the same extent as an ACE-inhibitor, without impairing left ventricular function, and was associated with a reduction of fibrosis [100].

Clinical investigations

Clinical studies have been performed to investigate the pharmacokinetic and pharmacological profile of the CCA mibebradil in humans. Pharmacokinetic experiments demonstrated that mibebradil is a lipophilic compound that is strongly bound to α1-acid glycoprotein (> 99.5%) following rapid absorption after oral administration [101]. The clearance of mibebradil after multiple doses is about 150 ml/min and independent of the dose. Volume of distribution at steady state is larger than the plasma volume and ranges from 130–220 l. The high plasma-protein binding of the drug indicates an extensive distribution into peripheral tissues. After hepatic biotransformation the inactive metabolites of mibebradil were excreted to 75% in the bile and to 25% in the urine [102]. The pharmacokinetic properties of mibebradil are characterized by a high bioavailability (90% at therapeutic doses) and a long plasma half-life (17–25 hours). Food has no effects on the rate or extent of mibebradil absorption. Steady state is reached within 3–4 days, and the inter- and intra-patient variability of plasma concentration is low. A strong correlation exists between the plasma concentration of mibebradil and its effects, while the drugs pharmacokinetic characteristics are not affected by demographic factors, eg, age, gender, race, weight and renal function. Mibebradil is well tolerated, exerts a long duration of action and a smooth effect during the 24-hours dosing interval allowing once a day dosage.

The efficacy of mibebradil in hypertensive patients

The tolerability and hemodynamic and humoral effects of mibebradil were investigated in a double-blind, placebo-controlled study [103]. In this dose-finding study 64 patients with hypertension received oral doses of 50, 100, 150, or 200 mg/kg/d mibebradil in a solution for 8 days. At day 1 and 8 of the active treatment interval a complete blood pressure profile was measured. As a result of this study blood pressure was dose-dependently reduced over the full 24 hour dosing period with more pronounced effects on day 8 than on day 1 explained by the pharmacokinetic profile of the drug (plasma half-life 17–25 hour, 3–4 days to steady-state conditions). The maximum blood pressure reduction was obtained after 150 mg/kg (supine blood pressure, -34/-25 mmHg). Despite a slight decrease in supine heart rate cardiac output was increased. PQ time was dose-dependently increased and concentration-effect analysis showed that relevant AV conduction disturbances occur only at concentrations much higher than those required to reduce blood pressure (figure 11). Changes in catecholamines, plasma renin activity, and aldosterone were small and inconsistent. Mibebradil was well tolerated up to 150 mg/kg and no relevant side effects were obtained, but treatment was stopped in one patient in the 200 mg/kg group because of bradycardia. Finally, mibebradil has a long-lasting antihypertensive effect after once-daily administration with the minimal effective dosage 50 mg/kg and the maximal 100 mg/kg.

These findings are in agreement with the results of another dose-finding, multicenter, double-blind, placebo-controlled study [104]. In this study 202 patients with mild-to-moderate hypertension were randomized to receive doses of 25, 50, 100, or 150 mg/kg/d mibebradil for 4 weeks. Blood...
Figure 11. Time courses of blood pressure, heart rate, PQ time, and change of cardiac output on day 1 (left panel) and day 8 (right panel) in patients with hypertension after oral administration of mibefradil given once daily as drinking solution (○ indicates placebo (PL), ▲ indicates 50 mg/kg, ● indicates 150 mg/kg, ■ indicates 200 mg/kg mibefradil). Data are shown as mean ± SEM.
pressure and heart rate were measured at trough and peak at the end of the four weeks of the placebo run-in-phase and at the end of the first, second and fourth week of the active treatment period. A significant dose-dependent drop in diastolic and systolic blood pressure was observed at trough and peak in all mibefradil treated groups with a trough-peak ratio greater than 0.8 indicating a high response rate. The full antihypertensive effect of mibefradil was achieved within 1–2 weeks and was associated with a slight dose-dependent decrease in heart rate and increase in PQ time. Clear dissociation was observed between the effects on blood pressure and PQ time when concentration-effect relationships were evaluated. Three patients of the 150 mg/kg mibefradil group were excluded from the study because of incidence of an adverse event. In conclusion, mibefradil was well tolerated with effective antihypertensive action.

In summary, investigations performed on healthy volunteers and hypertensive patients demonstrated that mibefradil is a potent vasodilator, lacks negative inotropic effects at therapeutic concentrations, does not exhibit reflex tachycardia during vasodilation and actually slightly decreases heart rate (approximately 8 beats/min with a dose of 100 mg/kg in humans). These effects probably result from the inhibition of Ca$^{2+}$ influx through L- and T-type calcium channels by mibefradil on the sinus atrial and AV nodes. The drug does not appear to cause constipation and has a low incidence of ankle oedema. Mibefradil exerts a higher selectivity for the coronary arteries compared to the peripheral vasculature.

Mibefradil in comparison to other antihypertensive drugs

Some studies were performed to compare the antihypertensive effects of mibefradil with those of other antihypertensive drugs. Using comparable doses of blood pressure reduction in patients with mild-to-moderate essential hypertension the onset of antihypertensive effects of a single dose of mibefradil (150 mg/kg/d) was slower than that of verapamil (240 mg/kg/d) or diltiazem (240 mg/kg/d). The differences from placebo in mean maximal PQ time prolongation was for mibefradil 15.6 ms compared to those of verapamil 44.0 ms and diltiazem 56.0 ms [105]. The decrease in heart rate was similar to those of verapamil or diltiazem. The antihypertensive actions of 50 or 100 mg/kg mibefradil were compared to those of 5 or 10 mg/kg amlodipine in patients with mild-to-moderate essential hypertension. After 12 weeks of once-daily treatment both long-acting calcium antagonists showed similar blood pressure reducing effects. Patients on mibefradil had a decrease in heart rate of 5.5 bpm, whereas patients on amlodipine had no changes in heart rate [106]. The antihypertensive effect of mibefradil (50–100 mg/kg) was compared with that of enalapril (20–40 mg/kg) in 187 patients with mild-to-moderate hypertension (Hoffmann La Roche, in preparation). Results of this study demonstrated that both drugs induced a similar decrease in sitting diastolic and systolic blood pressure. The response rates (reduction of sitting diastolic blood pressure to ≤ 90 mmHg) was 81 % for mibefradil and 74 % for enalapril (no significance). The antihypertensive efficacy and dose-response characteristics of mibefradil (12.5, 25, 50, 100 mg/kg) in combination with a diuretic treatment regime (hydrochlorothiazide 25 mg/kg/d) were investigated in 107 patients with mild-to-moderate essential hypertension [107]. After eight weeks of combined treatment an additional effect of both drugs in the reduction in sitting diastolic and systolic blood pressure at trough was measured. The dose-related decrease in blood pressure was significantly different in patients treated with 50 and 100 mg/kg mibefradil as compared to hydrochlorothiazide treatment alone.

Mibefradil in the therapy of stable angina pectoris

The antiischaemic and antianginal effects of mibefradil have been evaluated in several clinical studies in patients with chronic stable angina pectoris. In one double-blind, placebo-controlled dose-finding study 65 patients with stable effort-induced angina pectoris were randomized to receive a single oral dose of 50, 100 or 200 mg/kg mibefradil given in a solution [98]. Measured parameters were left ventricular ejection fraction (LVEF), blood pressure, and heart rate at rest and during supine bicycle exercise test. As results of this study mibefradil increased exercise duration, time to 0.1 mV ST-segment depression, time to angina, and decreased maximum ST-segment depression and improved resting LVEF (figure 12). These effects were dose dependent. No signs of negative inotropy were noted and the drug was well tolerated. In another multicenter, double-blind, placebo-controlled, parallel design dose-finding study 126 patients with chronic stable angina pectoris were randomized to receive 25, 50, 100, and 150 mg/kg mibefradil [108]. Here, mibefradil exerted a dose-dependent decrease in heart rate and blood pressure and plasma concentrations > 300 ng/ml. The therapeutic response rate concern-
ing the increase of exercise duration up to 1 minute was in the placebo-group 19 % and in the 25, 50, 100 and 150 mg/kg mibe-
fradil treated groups 40 %, 36 %, 68 % and 65 %. Most adverse
events were first-degree of AV-block (8 %) and dizziness (7 %).

These facts are supported by a multicenter, double-blind,
placebo-controlled, parallel-design trial on 126 patients with
chronic stable angina pectoris receiving 25, 50, 100 and 150
mg/kg mibefradil for two weeks [109]. Ambulatory 48 hours
electrocardiographic monitoring (ECG) was performed at the
end of the 1 week placebo run-in phase and after the active
treatment period. In this study mibefradil was associated with
less incidences of ischaemic episodes and ischaemia duration than
manifested during ambulatory ECG monitoring in lin-
eral dose-response relation (figure 13). Doses of 150 and 100
mg/kg of the drug resulted in a 73 % and 63 % reduction in the
frequency of episodes of ST-segment depression and a 78 % and 58 % reduction in the total duration of ST-segment
depression. Dose-dependent ECG abnormalities related to
treatment were first-degree of AV block, sinus bradycardia and short Wenckebach episodes observed during sleep on Holter monitoring.

Comparison of the antianginal effects of mibefradil
with other drugs
The antianginal and antiischaemic effects after long-term
treatment with mibefradil and diltiazem were investigated in
patients with chronic stable angina pectoris [110]. After 12
weeks of treatment, both drugs induced equivalent mean in-
crease in exercise tolerance test duration of > 1 min and im-
provement in time to onset of angina and time to persistence
of ST-segment depression of 1 mm. In contrast to diltiazem,
a large reduction in heart rate, blood pressure, rate-pressure
product and cardiac workload were observed at each stage of
the exercise tolerance test among patients treated with
mibefradil. The combined therapy of 50 mg/kg once a day
mibefradil with an existing stable beta-blocker therapy pro-
duced additive antianginal and antiischaemic effects and was
well tolerated [111].

Efficacy of mibefradil in the therapy of congestive heart
failure
The MACH-1 study (Mortality Assessment in Congestive
Heart Failure Trail) will be performed to investigate whether
the addition of mibefradil to the standard therapy for heart
failure reduces mortality and symptoms in patients with symp-
omatic heart failure [112]. In this 125-center, double-blind,
placebo-controlled study 2400 patients with congestive heart
failure of NYHA classes II–IV were recruited who will be
followed for up to 3 years. At the end of the year 1999 the
results of this study will be published.

The effects of two i.v. doses of mibefradil (400 ng/ml and
800 ng/ml) comparable to the oral doses of 50 mg/kg and 100
mg/kg of mibefradil were studied in patients with heart fail-
ure to examine the index of left ventricular function and drug
plasma levels [113]. They found that 800 ng/ml i.v. mibefradil
decreased mean aortic blood pressure (-8.5 mmHg) and sys-
temic vascular resistance (-12 %) and also reduced end-systolic
stress and volume, thus improving ejection fraction (EF) (52 %
to 58 %). In patients with depressed EF the same dose still
decreased left ventricular systolic wall stress and improved
EF but also depressed the maximal first derivative of left ven-
tricular pressure, suggesting negative inotropy. Authors con-
cluded that high plasma levels of mibefradil might produce
myocardial depression in patients with heart failure, and cau-
tion should be exerted when mibefradil is used on a chronic
basis in patients with cardiac dysfunction (because of its long
half life). A study performed in 15 patients with heart failure
of NYHA class II or III for dyspnea and depressed EF < 40 %
due to a previous myocardial infarction demonstrated that
orally applied mibefradil caused no worsening of systolic
function and preserved diastolic function in short-term treat-
ment [114]. While amlodipine (10 mg/kg) increased only the
time to onset of anginal symptoms, mibefradil (100 or 150
mg/kg) increased exercise duration and the time to angina or
ST-segment depression [115]. Both parameters were increased
by mibefradil to a greater extent than amlodipine. In addi-
tion, the decrease in the number of asymptomatic episodes of
ischaemia during 48 hour ambulatory monitoring was greater
with mibefradil (-3.5) than with amlodipine (-1.5).

Drug-interactions of mibefradil
In general, mibefradil is metabolised by cytochrome P_{450-
mediated reactions. The enzymes cytochrome 3A4, 2D6 and
1A2 are competitively inhibited by mibefradil [116]. Thus,
drugs which are metabolised by these enzymes may interact
with mibefradil when administered concomitantly.

The pharmacokinetic and pharmacodynamic effects of
combined treatment with mibefradil and cyclosporin were
investigated in 6 stabilised renal transplant patients on long-
term oral cyclosporine therapy (twice daily) receiving oral
mibefradil (50 mg/kg for 1 week). Mibefradil led to a 2- to 3-
fold increase in plasma cyclosporin concentration [117], in-
...
Pharmacodynamic interaction has been reported between mibefradil and metoprolol in healthy volunteers resulting in a 2-fold increase in peak plasma concentrations of total metoprolol and about 4- to 5-fold increase in AUC [117]. Coadministration of terfenadine (60 mg/kg twice daily) with mibefradil in healthy volunteers caused an elevation in plasma concentrations of terfenadine, resulting in a 12 % increase in mean QR interval which can be associated with life-threatening arrhythmias [118]. Thus, combined therapy of mibefradil with terfenadine is contraindicated. A clinically significant pharmacokinetic interaction between mibefradil (100 mg/kg for 2 weeks) and simvastatin (once daily) has been reported associated with enhanced potential for adverse events [117].

In contrast, no clinically important pharmacokinetic or pharmacodynamic interaction has been reported between mibefradil and H2-blockers (cimetidine), antiarrhythmics (quinidine), digoxin, β-blockers (atenolol), angiotensin converting enzyme inhibitors (enalapril), diuretics, nonsteroidal antiinflammatory agents, long-acting nitrates, thio phylline or antithrombotic agents (acenocoumarol, phenprocoumon, warfarin) [116].

In summary, the inhibition of cytochrome P450-isoenzymes by mibefradil can decrease the metabolising capacity for some currently administered drugs metabolised by these enzymes. However, the potential to cause clinically significant alterations in the pharmacokinetic properties of several established agents has been reported by coadministration with other CCA.

Summary
Localization and functional importance of L-type calcium channels in the regulation of intracellular signalling pathways have been intensively investigated. These channels play an important role in the linking of electrical signals to contractile responses and transmitter release. The occurrence in excitable and smooth muscle cells of the cardiovascular system has rendered these channels as important targets for the development of cardiovascular drugs, the CCA. All three types of CCA, dihydropyridines, phenylalkylamines, and benzothiazepines, inhibit transmembrane Ca2+ entry into vascular smooth muscle and myocardial cells and their major action, vasodilatation of the arterial vasculature is often accompanied by several side-effects including negative inotropy, reflex tachycardia, headache, ankle oedema, constipation.

Observations from several experiments suggest that T-type calcium channels participate in the regulation of pathological alterations in the cardiovascular system (proliferation of muscle cells, hypertrophy of ventricular myocytes). Their localization in cells with spontaneous activity suggests a participation of this type of calcium channels in autonomous excitation. Mibefradil is a CCA featuring a selective blockade of T-type calcium channels but also some L-type calcium channel inhibiting actions and is characterized by relaxation of vascular muscle with preferential coronary vasodilatation, lack of negative inotropic action, reduction of heart rate, and antiischaemic effects. The selective blockade of vascular and cardiac T-type calcium channels by mibefradil is thought to be responsible for vascular protection and decrease of heart rate without negative inotropic action. Mibefradil is further distinguished by desired pharmacokinetic properties enabling treatment of cardiovascular diseases with high therapy safety and patient compliance, and improved relationship between risk and benefit. Clinical studies have demonstrated that mibefradil exerts long-acting antihypertensive effects using once-a-day dosing with the minimal effective dose being 50 mg/kg and the maximum dose being 100 mg/kg. In patients with generally mild-to-moderate hypertension oral mibefradil was superior to nifedipine and diltiazem and had similar efficacy to amlodipine. In the therapy of patients with chronic stable angina pectoris mibefradil increased dose-dependently the exercise duration, time to angina, and time to ST-segment depression indicating an antianginal and antiischaemic action of the drug. Its efficacy was similar to that of diltiazem and tended to be greater than that of amlodipine in patients with stable angina pectoris. Mibefradil was well tolerated and was associated with a lower incidence of leg oedema than amlodipine and nifedipine. However, CCA are a heterogeneous class and recent data support the safety of verapamil (DAWIT II) as well as the newer long-acting dihydropyridines amlodipine (PRAISE), felodipine (VHeFT III) and nisoldipine (DEFIANT II) in patients with myocardial infarction or congestive heart failure. The effects of mibefradil on symptoms and survival in patients with congestive heart failure are currently under investigation (MACH-I).

Addendum
This review article has been addressed to a better understanding of the full therapeutic spectrum of the calcium channel antagonist, mibefradil, within the cardiovascular system. Although this drug has been withdrawn from the market because of serious drug interactions but not because of its lack of cardioprotection, the concept of combined T-type and L-type calcium channel blockade remains novel and of potential clinical interest.

References
L-and T-type Ca²⁺ channel blockade by mibefradil


CA-ANTAGONISTS

L- and T-type Ca\(^{2+}\) channel blockade by mibefradil

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