Class IV antiarrhythmic agents: new compounds using an old strategy

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Running title: calcium channel antagonists in antiarrhythmic therapy

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Abstract

Cardiac arrhythmias are a major cause of morbidity and mortality in the industrialized world. Among their treatment regimens one can find the calcium channel antagonists (CCAs), the class IV agents. In the cardiovascular system L- and T-type calcium channels are found on vascular smooth muscle cells and cardiac myocytes with well defined physiological roles. Inhibition of calcium channels by CCAs has widely been used in clinical practice for several decades. Cardiovascular disorders are one of the many fields of medicine in which CCAs are used for various reasons and conditions. The three main indications of them are hypertension, angina and various cardiac arrhythmias. The most important classes of CCAs are dihydropyridines, phenylalkylamines and benzothiazepines but some newer compounds do not fall into any of these major classes. Dihydropyridines are not used in the antiarrhythmic therapy but are good vasodilators and antianginal agents. In contrast, phenylalkylamines and benzothiazepines exert cardiac actions in vivo and therefore these are one choice of antiarrhythmic drugs. This review focuses on phenylalkylamines, benzothiazepines and on new drugs with potential antiarrhythmic action in the heart as well as the mechanisms how calcium channels antagonism can lead to an antiarrhythmic action.

Keywords: action potential, antiarrhythmic drugs, benzothiazepine, calcium channel, calcium channel antagonist, cardiac arrhythmia, cardiac ion currents, phenylalkylamine

1. Introduction

Cardiac arrhythmias are a large group of conditions in which the normal, precisely timed electrical activity of the heart is perturbed. This group includes many, greatly diverse disorders from the reduction of electrical activity in sick sinus syndrome or various forms of bradycardia through the single supraventricular or ventricular extrasystoles to the life-threatening tachyarrhythmias like ventricular fibrillation (VF). The most common form of arrhythmias is atrial fibrillation (AF) which does not usually lead to sudden cardiac death but its complications can be severe [1]. Sudden cardiac death is often a consequence of VF which occurs mostly on the ground of ischemic heart disease [2] and is a major cause of mortality in Europe and the USA [3]. In the management of cardiac arrhythmias pharmacological treatment is used beside electrical interventions as catheter ablation. In the former the arsenal of drugs keeps continuously increasing but according to the probably most commonly used classification they belong to one of the five major groups of the Vaughan Williams classification [4]. Drugs that reduce the ionic current flowing through calcium channels, the calcium channel antagonists (CCAs) fall into class IV of this classification. CCAs are being used in clinical practice for a long time now and not only in cardiovascular disorders. The three main indications of CCAs are hypertension, angina and various cardiac arrhythmias in cardiology. The most important classes of CCAs are dihydropyridines, phenylalkylamines and benzothiazepines but some newer compounds do not fall into any of these major classes.

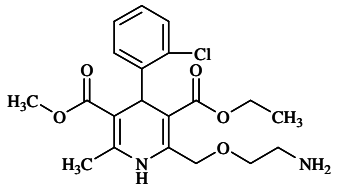
Calcium channels are found on almost every cell in the human body and classified to various types including L-, N-, P/Q-, R-, and T-types. These channel proteins have several subunits and the α_1 subunit is the pore forming one among them, whereas others (α_2, β, γ, and δ) also have well defined roles [5]. In vascular smooth

muscle cells (SMCs), the L-type channels ($Ca_v1.2$) whereas in cardiac cells in adulthood, both L- ($Ca_v1.2$ and to a lesser extent $Ca_v1.3$) and T-types ($Ca_v3.1$ and $Ca_v3.2$) are found; the latter ones present only in nodal tissues with pacemaker activity. Their function is essential in the maintenance of vascular tone and contraction in arterioles, for the impulse generation and propagation in nodal tissues and last but not the least, for contraction of working myocardium [5]. This review focuses on the evidence of antiarrhythmic actions of some CCAs, the potential mechanisms leading to this beneficial effect, the comparison of actions of various CCAs and a structure-activity relationship of the presented CCAs.

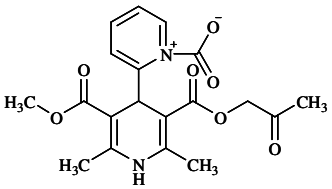
2. Dihydropyridines (a large class of CCAs with no antiarrhythmic activity)

Dihydropyridines (**Fig. 1.**) are only mentioned very briefly for the sake of completeness as these are one of the three major classes of organic CCAs. Dihydropyridines are not used in the antiarrhythmic therapy due to their high vascular over cardiac selectivity [6]-[7]. Mechanisms of this vascular selectivity include at least two factors. One is the well known voltage- and use-dependent L-type channel inhibition [10] which taken together with the fact that SMCs are more depolarized compared to myocardium results in a higher inhibition of calcium channels in SMCs. Another mechanism is the different isoform of α_1 in SMCs and myocardium and the observation that the smooth muscle isoform expressed in CHO cells is more sensitive to inhibition by neutral dihydropyridines but not by verapamil [9].

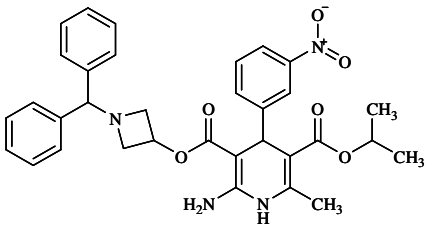
Dihydropyridines are good vasodilators and often used in combination with other hypertensive agents [11]. Dihydropyridines are also useful as antianginal agents [12]. The short acting dihydropyridines are more likely to cause sudden vasodilatation than those with longer onset and duration of action and therefore short acting ones more likely evoke stimulation of the sympathetic nerves leading to reflex tachycardia [13], [14]. This action is not beneficial especially in hypertensive patients with angina and ischemia where the further increase in myocardial oxygen requirement should be avoided.



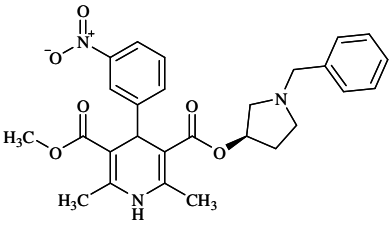
* Amlodipine



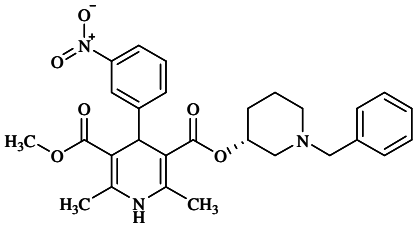
Aranidipine



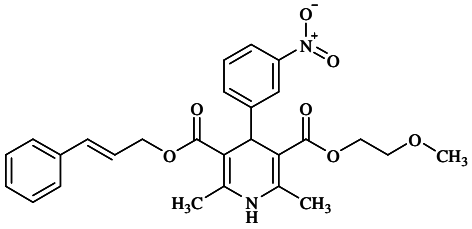
* Azelnidipine



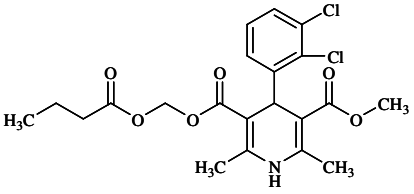
Barnidipine
Mepirodipine



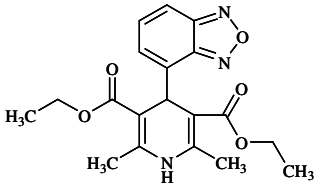
Benidipine



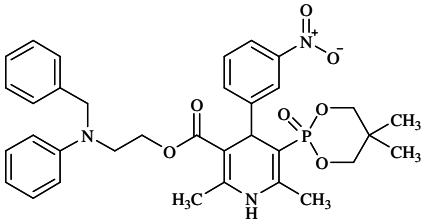
Cilnidipine



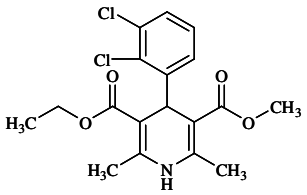
Clevidipine



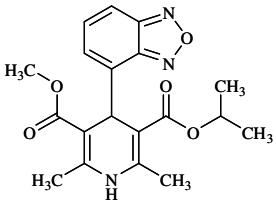
Darodipine



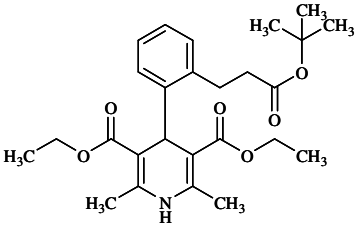
Efonidipine
NZ-105



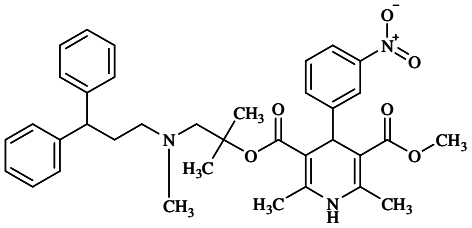
* Felodipine



* Isradipine
PN 200-110



Lacidipine



* Lercanidipine

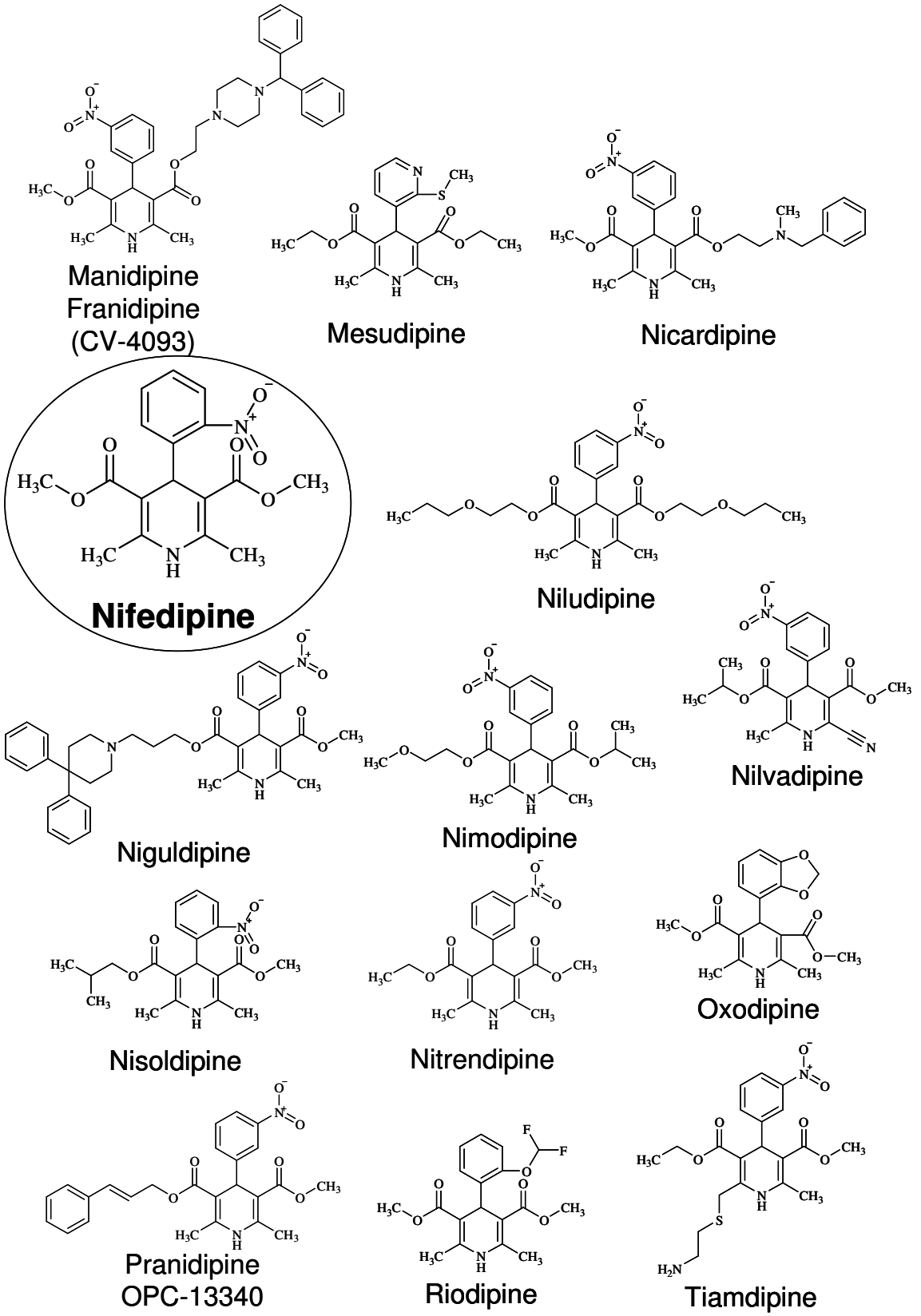


FIG. 1. Chemical structure of dihydropyridines. The first and best known one is the circled nifedipine. Those compounds marked with asterisks are the long acting ones.

3. The calcium channel inhibitory actions of some CCAs

3.1. Actions on the L-type calcium channels

CCAs usually exert a use-dependent inhibition on L-type Ca^{2+} channels ($I_{Ca,L}$) as it was described with verapamil in rat ventricular myocytes [15]. Similar observation was made with D600 (gallopamil) in rabbit and feline ventricular muscle [16], with tiapamil (RO 11-1781) in guinea-pig urinary bladder SMCs [17] and with diltiazem in human atrial and ventricular myocardium [18] as well as in rat aorta SMCs [19]. Not only use-, but voltage-dependent inhibition was observed with tiapamil in guinea-pig urinary bladder SMCs [17] and diltiazem in human atrial and ventricular myocardium [18]. It was suggested that verapamil blocked more effectively the inactivated channels [15] and also that it preferentially acted on the open state of the channels [19] similarly to diltiazem. The effectivity of phenylalkylamine and benzothiazepine type CCAs on L-type calcium current ($I_{Ca,L}$) is compared in Tables 1 and 2.

TABLE 1. The half-inhibitory concentrations (IC_{50}) of phenylalkylamine CCAs (**Fig. 2.**) on $I_{Ca,L}$.

DRUG	IC_{50} value	Holding potential	Species/preparation	Reference
Verapamil	less than 100 nM	-40 mV	guinea-pig/ventricular myocytes	[20]
	246 nM	-50 mV	rat/ventricular myocytes	[21]
	900 nM	-80 mV, followed by a 20 ms long -40 mV prepulse	rat/ventricular myocytes	[15]
	600 nM	-60 mV	rat/aorta SMCs	[19]
D600 (gallopamil)	1 μM	-40 mV	guinea-pig/ventricular cells	[20]
	less than 1 μM	-60 mV	frog/atrial cells	[22]
	less than 1 μM	-60 mV	cat/ventricular muscle	[23]
Tiapamil (RO 11-1781)	around 1 and 20 μM	-45 and -65 mV	guinea-pig/urinary bladder SMCs	[17]

TABLE 2. Benzothiazepine CCA (**Fig. 3.**) effects on $I_{Ca,L}$ and contractions.

DRUG	IC_{50} value or percentage reduction / holding potential	Species/preparation	Reference
Diltiazem	512 nM in reduction of $I_{Ca,L}$ / -50 mV	rat/ventricular myocytes	[21]
	630 nM in reduction of $I_{Ca,L}$ / -50 mV	guinea-pig/ventricular cells	[24]
	500 nM in reduction of $I_{Ca,L}$ / -40 mV	ferret/right ventricular papillary muscles	[25]
	3 µM in reduction of $I_{Ca,L}$ / -60 mV	rat/aorta SMCs	[19]
	300 µM in reduction of I_{Ba} / -60 mV	rabbit/mesenteric artery SMCs	[26]
	694 nM in reduction of tension	human/coronary artery	[27]
	277 nM in reduction of tension	rabbit/aorta	[28]
	25 % reduction of contractile force by 10 µM	rabbit/atrial muscle	[29]
	25 % reduction of calcium-evoked contraction by 1 µM	sheep/cerebral artery	[29]
	25 % reduction of calcium-evoked contraction by 80 nM	sheep/depolarized coronary artery ring	[30]
	120 nM on reduction of potassium-induced contraction	rat/thoracic aorta	[31]
	over 10 µM on vasodilatation of phenylephrine precontracted vessels	rat/thoracic aorta	[31]
Clentiazem (TA-3090)	30 µM in reduction of I_{Ba} / -60 mV	rabbit/mesenteric artery SMCs	[26]
	221 nM in reduction of tension	human/coronary artery	[27]
	61 nM in reduction of tension	rabbit/aorta	[28]
Siratiazem (LR-A113)	25 % reduction of contractile force by 10 µM	rabbit/atrial muscle	[29]
	25 % reduction of calcium-evoked contraction by 1 µM	sheep/cerebral artery	[29]
	25 % reduction of calcium-evoked contraction by 130 nM	sheep/depolarized coronary artery ring	[30]
S-2150	190 nM on reduction of potassium-induced contraction	rat/thoracic aorta	[31]
	29 nM on vasodilatation of phenylephrine precontracted vessels	rat/thoracic aorta	[31]

Molecules with structures different from both phenylalkylamines and benzothiazepines (and also from dihydropyridines) can also inhibit $I_{Ca,L}$. Some of these (**Fig. 4.**) can show some structural similarity to one (or more) of the major groups of CCAs but some are completely different without any sign of structural similarity (**Fig. 5.**). The IC_{50} values of these substances are summarized in Table 3. On top of the concentration-dependent inhibition of $I_{Ca,L}$ many of these drugs had additional effects on the kinetics of $I_{Ca,L}$.

Semotiadil shifted the voltage-dependent inactivation curve to the left and accelerated the decay of the current in concentrations higher than 1 µM. At 1 µM it also slowed the recovery from inactivation. Long-lasting inhibition of $I_{Ca,L}$ after removal of semotiadil may be due to tight binding of semotiadil on the channel through a hydrophobic site [32]. Levosemotiadil also shifted the steady-state inactivation curve to more negative potentials [33] just as it was observed with fantofarone [34] as well as with bepridil [35]. Fantofarone blocked $I_{Ca,L}$ in a voltage-dependent manner in rat ventricular myocytes, and evoked both tonic and use-dependent blockade of $I_{Ca,L}$ [34]. The voltage-dependent inhibition of $I_{Ca,L}$ was detected with SR33805 [36] and bepridil [37]. Inhibition of $I_{Ca,L}$ by 5 µM AH-1058 had both tonic (25 % reduction) and use-dependent component (further 60% reduction) [38]. Bepridil slowed the recovery from inactivation of $I_{Ca,L}$ [35].

TABLE 3. The inhibitory potency of other CCAs (**Fig. 4 and 5.**) on $I_{Ca,L}$.

DRUG	IC_{50} value / holding potential	Species/preparation	Reference
Semotiadil (SD-3211)	between 10 and 100 µM / -80 mV followed by a 50 ms long -40 mV prepulse	guinea-pig/ventricular cells	[39]
	84, 900 and 2000 nM / -60, -80 and -100 mV	rabbit/portal vein SMCs	[32]
Levosemotiadil (SD-3212)	1.3 µM / -40 mV	guinea-pig/atrial cells	[33]
Fantofarone (SR 33557)	22 nM and 9 µM / -50 and -80 mV	rat/ventricular myocytes	[34]
	1.4 and 150 nM / -40 and -80 mV	mouse/cardiac cells in primary culture	[36]
SR 33805	4.1 and 33 nM / -40 and -80 mV	mouse/cardiac cells in primary culture	[36]
	24 nM / -80 mV	rat/ventricular myocytes	[40]
BRL-32872	2.8 µM / -50 mV	guinea-pig/ventricular cells	[41]
KT-362	28.6 % reduction in 7 µM / -40 mV	dog/Purkinje cells	[42]
Monatepil (AJ-2615)	18.7 nM / -40 mV	guinea-pig/ventricular cells	[43]
Bepridil	2.6 µM / -70 mV followed by a -40 mV prepulse	guinea-pig/ventricular cells	[44]
	0.5 µM / -50 mV	guinea-pig/ventricular cells	[35]
	1.55 µM / -40 mV	guinea-pig/atrial cells	[33]
AH-1058	0.32 and 4.91 µM / -40 and -80 mV	guinea-pig/ventricular cells	[45]

3.2. T-type calcium channel inhibition of CCAs

Mibefradil (**Fig. 5.**) is usually regarded as a selective inhibitor of the T-type calcium channels ($I_{Ca,T}$). Later it turned out that it is not entirely specific as $I_{Ca,L}$ is also reduced by mibefradil. Martin *et al.* review the literature and list these actions of the drug. Usually the inhibitory effect of mibefradil on native $I_{Ca,T}$ is more potent compared to that on native $I_{Ca,L}$ by 13-70, 17 and 3 times in vascular smooth muscle, atrial myocytes and human myoblasts, respectively [46]. Mibefradil blocked 2-3 times more potently $I_{Ca,T}$ compared to that of $I_{Ca,L}$ in guinea-pig ventricular myocytes [47]-[49] but 30 times more potently in rat ventricular cells [50]. In contrast, in rabbit sinoatrial (SA) node cells 1 µM mibefradil reduced $I_{Ca,T}$ less than $I_{Ca,L}$ (by 55 and 64 %, respectively) [51]. Regarding the mibefradil inhibition of $I_{Ca,T}$ and $I_{Ca,L}$ some found that only the latter one was blocked strongly in a voltage- and use-dependent manner [49]. In contrast, in rat ventricular cells both $I_{Ca,T}$ and $I_{Ca,L}$ was reduced by mibefradil in a voltage- and use-dependent manner [50]. In canine Purkinje fibers mibefradil blocked calcium currents and in the presence of 1 µM mibefradil the T/L current ratio was reduced. The steady-state activation half-potentials were shifted to the left by 40 and 10 mV for $I_{Ca,L}$ and $I_{Ca,T}$, respectively [52]. Compared to other CCAs, mibefradil was less potent than verapamil in inhibiting calcium current in isolated guinea-pig myocytes [53]. The inhibitory action of mibefradil on $I_{Ca,T}$ was approximately twice more potent compared to that of $I_{Ca,L}$ [47].

Not only mibefradil blocks $I_{Ca,L}$ in addition to $I_{Ca,T}$ but other CCAs also reduce $I_{Ca,T}$ on top of the $I_{Ca,L}$. Verapamil block of $I_{Ca,T}$ was observed in guinea-pig ventricular cells (10 % reduction by 1 µM, same extent as in $I_{Ca,L}$) [47] and in rat aorta SMCs (IC_{50} of 30 µM) which showed no use-dependence [19]. In contrast, stably expressed human $Ca_v3.1$ T-type channels in human embryonic kidney (HEK) cells were blocked by verapamil in a use- and voltage-dependent manner with an IC_{50} of 21.4 µM and the drug significantly slowed the recovery from inactivation. It was suggested that verapamil achieves its inhibitory effect via occlusion of the channel pore associated with an open/inactivated conformation of the channel [54].

10 µM diltiazem (which reduced $I_{Ca,L}$ by 18 %) had no action on T-type calcium channels in guinea-pig ventricular myocytes [47] but in rat aorta SMCs it reduced $I_{Ca,T}$ with an IC_{50} of 30 µM, ten times less potently than $I_{Ca,L}$. Diltiazem, similarly to verapamil, preferentially acted on the open state of the L-type calcium channel and on the resting and inactivated states of the T-type calcium channel [19].

Bepridil reduced $I_{Ca,T}$ in a voltage-independent manner in guinea-pig atrial myocytes; therefore at normal diastolic potentials (~-90 mV) it actually reduced $I_{Ca,T}$ more potently than $I_{Ca,L}$ [37]. In contrast, block of $Ca_v3.2$ channels (underlying $I_{Ca,T}$) in HEK cells was voltage-dependent but frequency-independent. IC_{50} yielded 0.4 μM at -70 mV holding potential (26 times lower than at -100 mV). Bepridil (10 μM) shifted both steady-state activation and inactivation to more negative potentials but did not affect the recovery kinetics [55].
Within the reviewed CCAs there are some without major inhibitory action on $I_{Ca,T}$ like D600. 1 μM D600 (causing complete inhibition of $I_{Ca,L}$) did not reduce $I_{Ca,T}$ in rabbit SA cells [56]. In primary cultured murine cardiac cells $I_{Ca,T}$ was not reduced by either 100 nM fantofarone or 100 nM SR 33805 [36].

4. Structure-activity relationship of CCAs

4.1. Benzothiazepines

Benzothiazepines are one of the three major classes of CCAs which exert a functional state-dependent inhibition of the L-type calcium channel (inactivated>open>closed) [57]. High affinity binding of benzothiazepines requires Ca^{2+} bound to the channel [57]. On the contrary, increased concentration of Ca^{2+} antagonize diltiazem block of the channels in both heart [58] and smooth muscle [59]. The extracellular application of benzothiazepines effectively blocks the L-type Ca^{2+} channel but the intracellular application does not secure the inhibitory effect. This led to the conclusion that benzothiazepine block is mediated from the extracellular side of the channel pore [60], [61]. These findings were found plausible by Monte Carlo simulation [57]. The pathway leading to the binding site of the inner pore of the channel was found to be wide enough for the molecule to "penetrate" [62]. Despite these concurrent results, the quaternary ammonium derivative of diltiazem was found to be able to inhibit the L-type channels from the intracellular side [63].

The presence of Ca^{2+} is an important factor in ligand-channel binding. The Ca^{2+} in the selectivity filter was found to bind not only to the carbonyl groups of benzothiazepine but also to the glutamates of the selectivity filter [57]. In the absence of calcium ions the amino group of benzothiazepine molecule interacts with the previously mentioned glutamates directly [57]. The interaction of the aromatic rings with the Y4i11, F3i22 and F3p49 residues is also important [57]. Substitution in position 3 of the 7 member heteroatomic ring has only moderate effect on benzothiazepine binding. However, this side group should be preferably hydrophobic to increase the inhibitory action [64]. The length of the alkyl chain between the nitrogen atoms does not influence the binding of the benzothiazepine to the channel [57]. Benzothiazepine interaction with a closed calcium channel was destabilized due to loss of contact sites at the C terminal of the inner helices [57]. Systematic point mutation of the amino acids in domains IIIS6 and IVS6 highlighted the essential residues for the diltiazem block, for instance I1150, I1156 and M1160 in IIIS6 as well as I1460 and M1464 in IVS6 [65].

The Ca^{2+} channel inhibitory and hypotensive effects of the derivatives of diltiazem were also investigated in several articles. Clentiazem (8-chloro-diltiazem) was also found to be able to reduce peripheral arterial resistance [66]. Assumingly, this effect mediated by the same manner as L-type Ca^{2+} channel inhibition by diltiazem. In S-2150 the dimethyl amino group was replaced by a complex (2-methoxyphenyl)-1-piperazinyl substituent. The nitrogen atoms in the piperazinyl ring may have the same effect as the amine nitrogen in clentiazem. The connecting ethylene chain was increased to propylene group, but this does not seem to have an effect on calcium channel inhibition (see above) [57]. The additional methoxy group probably plays a role in calcium chelating just like in the phenylalkylamines [67]. This molecule found to be less cardio-depressive than diltiazem [68] but its hypotensive effect is 4-7 times more potent than that of diltiazem [31]. This different vascular over cardiac selectivity may come from the wide spectra of the effects of benzothiazepine and derivatives, which are not just restricted to the L-type Ca^{2+} channel inhibition [69]. Siratiazem hardly differs from diltiazem as just one of the methyl groups was substituted to isopropyl group. This modification might mimic one of the essential parts of verapamil binding properties [70]. Semotiadil (SD-3211) and its S-enantiomer sesamodil (levosemotiadil, SD-3212) can both inhibit potassium depolarization-induced cytosolic Ca^{2+} increase in rat aorta [71]. We classified these two molecules as benzothiazepine-like compounds despite the smaller (only six member) heteroatomic ring containing the sulphur and nitrogen atoms. This might alter the Baeyer tension of the ring. These compounds also contain motifs similar to phenylalkylamines such as tertiary amine nitrogen and methoxy group attached to an aryl ring [67].

4.2. Phenylalkylamines

Articles described the mechanisms of verapamil binding to a synthetic channel peptide (SCP), which has authentic functional properties as the L-type Ca^{2+} channel [67]-[70]. Verapamil binds snugly to the pore of the channel in a folded conformation. Based on the Monte Carlo method with energy minimization, they showed that two important parts of the verapamil take part in the Ca^{2+} channel blocking action. Firstly the dimethoxy-phenyl

groups are bound with two Ca^{2+} ions coordinated to the acidic residues of the channel pore [67]. That is how a ternary complex is formed involving the channel, the ions and the antagonist. The second is the isopropyl group of verapamil which interacts with the four Ile residues of the channel constituting the putative gate of the SCP [67]. Other authors claim that isopropyl group of devapamil reaches the T2p48 and F3p49 residues [72]. Another study showed that verapamil, similarly to D600, blocked L-type Ca^{2+} channel only if applied from the extracellular side [73]. In contrast, others found that both D600 and verapamil are able to reduce action potential duration (APD) and plateau potential of cardiac AP dose-dependently, regardless of the intra- or extracellular application in isolated guinea-pig ventricular myocytes [74]. D600 (often mentioned as gallopamil) only differs from verapamil by an addition of a methoxy group to that aryl ring which is located closer to the nitrile group. This may increase the Ca^{2+} chelating effect of the molecule, or the number of available sites for hydrogen bond formation [75]. Anipamil was designed to be less hydrophilic and binding studies showed that anipamil, although binds tightly to cardiac membranes, its binding to the D888 (desmethoxyverapamil) binding sites is less potent compared to verapamil [76]. The number of methoxy groups was halved on each aromatic ring, and the isopropyl group was substituted with a longer, linear dodecyl group. These changes resulted in the decrease of the inhibitory potency, but prolonged effects [76]. Tiapamil misses the isopropyl [70] and the nitrile group [77] existing in both verapamil and D600. These functional groups considered as important channel-ligand interaction sites [72]. In spite of these preconceptions, two oxygen atoms from the bulky saturated six-membered ring interact with the calcium ion in the pore [72]. Nadler and his coworkers thoroughly investigated the electrophysiological effects of BRL 32872 and its synthetic derivatives. These compounds blocked the ion channels responsible for the rapid component of the delayed rectifier potassium current (I_{Kr}) on top of L-type calcium channels [78]. The authors stated that the hydrogen bond formation, the nitrogen substituted with aliphatic alkyl chains, but not the quaternization of nitrogen and the aromatic substitution are crucial for the inhibitory effect. The too long aliphatic nitrogen substitution decreases the activity of the molecule, which also supports the result of Dillon and his coworkers [76]. Fantofarone and SR 33805 show strong structural similarities to each other such as dimethoxy substituted aryl rings, nitrogen substituted with three aliphatic alkyl chain, isopropyl and sulfonyl groups. The role of these functional groups (except the sulphonyl group) is presumably the same as mentioned earlier in this chapter [67],[70],[78]. The sulfonyl group might participate in chelating the Ca^{2+} similarly to that mentioned with tiapamil [72]. SR 33805 was shown to inhibit competitively [3H]fantofarone, while allosterically [3H](+)-PN200-110, [3H](-)-D888 and cis-(+)-[3H]diltiazem binding to cardiac sarcolemmal membranes. This suggests that, just as fantofarone, it binds to a site different from that of dihydropyridines, phenylalkylamines and benzothiazepines [79].

4.3. Other compounds

The structure-activity relationship of the following compounds is based on the findings described in the previous two sections.

KT-362 shows motifs from both phenylalkylamine and benzothiazepine structure elements. It “inherited” the heteroatomic ring of the benzothiazepines, however, that ring is more substituted in diltiazem. It also contains methoxy groups attached to an aryl ring, resembling phenylalkylamines [67]. The distance between the two mentioned functional groups might seem enough for the molecule to undergo the necessary conformational changes to interact with both benzothiazepine and phenylalkylamine binding sites of the channels. However, the benzothiazepine and phenylalkylamine binding sites partially overlap with each other [65].

In this review some other compounds are also mentioned which can not be categorized clearly into any of the three major classes based on their chemical structure. These contain some structural motifs which presumably have the same function as the motifs mentioned earlier related to the major classes of the Ca^{2+} channel blockers.
Mibefradil binds to the same binding site in cardiac membranes as verapamil and with a similar potency [80]. Mibefradil has the isopropyl group [67], the tertiary amine, and the Ca^{2+} chelating ester group. These functional groups might seem enough to interact with both the channel and the ion [78]. But according to our assumption, the orientation of these groups prevents the strong inhibition of the voltage-gated L-type Ca^{2+} channel. Monatepil has a sulphur-containing heteroatomic ring, but that contains no nitrogen. Instead, the “expected” nitrogen can be found in the amide group attached to this ring. This amide might chelate a Ca^{2+} ion, but not as strong as an ester group. The other parts of the molecule do not resemble any other aforementioned functional groups except the same piperazinyl ring which can be found in S-2150. Due to the above mentioned observations about the chemical structure, monatepil seems to be less potent as a Ca^{2+} channel inhibitor as S-2150. Bepridil has an isobutyl ester which might take the role of the isopropyl group mentioned above, but due to the low number of hydrophilic groups, the interaction between bepridil and Ca^{2+} is not plausible. Owing to the lack of Ca^{2+} chelating activity, it cannot be an effective L-type channel inhibitor [67]. AH-1058 is quite the opposite, thanks to the adjacent methoxy and nitro groups attached to an

aryl ring, the molecule can bind Ca^{2+}. On the other hand, there are no molecular interaction sites binding to the channel itself. The structure of AP-792 shows absolutely no similarity to those mentioned in earlier sections.

5. Interactions between simultaneous binding of different inhibitor classes (allosteric model)

Nifedipine and verapamil inhibit the clentiazem binding to Ca^{2+} channels [81]. Binding studies showed a concentration-dependent positive allosteric interaction between [3H](+)-isradipine and mibefradil, but not with [3H](+)-isradipine and D600 enantiomers. Molecular and functional evidences point to an interaction between a dihydropyridine and mibefradil [82]. Semotiadil has a strong negative allosteric interaction with the three major classes of CCAs at their specific binding sites [83]. Based on radio ligand assays, verapamil inhibited binding of isradipine, but diltiazem stimulated the binding of isradipine in a temperature-sensitive manner [84]. Those binding residues being critical for the contact of the ligand receptor interactions are listed by Hockerman and coworkers [65]. Binding of diltiazem to L-type Ca^{2+} channels requires those residues overlapping with critical ones for dihydropyridine and phenylalkylamine block as well as residues unique to diltiazem. Channel-ligand interactions involve also residues which are only take part in binding one antagonist of the three major classes [65]. These facts indicate that the binding of the antagonists dynamically changes the binding regions of the L-type Ca^{2+} channel (mainly residues in IIIS6 and IVS6). Therefore, the binding of another class of CCA to the channel is altered. This was summarized in the allosteric model involving interactions between different binding sites [85].

6. Potential mechanisms behind the antiarrhythmic actions of CCAs

CCAs can induce antiarrhythmic action by several mechanisms.

1. Calcium overload occuring during cardiac ischemia [86] can lead to spontaneous Ca^{2+} release from the sarcoplasmic reticulum [87],[88]. This released Ca^{2+} is replaced by Na^+ by the forward mode of the Na^+/Ca^{2+} exchanger leading to the depolarization of the cell membrane [89]. This depolarization is called either early or delayed afterdepolarization (EAD or DAD) depending on their timing compared to the full repolarization of the cell membrane. EADs form before, while DADs are generated after the full repolarization [90]. These afterdepolarizations are well known triggering sources of cardiac arrhythmias. Large enough afterdepolarizations occurring in the vulnerable period (when those ion channels responsible for the upstroke of the AP can be opened) can evoke a triggered AP. This AP can manifest in a simple extrasystole but can be the trigger for a much more dangerous (sometimes lethal) rhythm disorders including torsade de pointes (TdP) type VF [91].

The reduction of inward calcium currents by CCAs (due to the inhibition of both L- and T-type calcium channels) results in reduced calcium influx to cardiomyocytes, therefore leading to calcium depletion, which according to the previous fact can have antiarrhythmic effect by reducing the risk of calcium overload. Verapamil was shown to suppress spontaneous or epinephrine-induced EADs and TdP in cats [92] and it suppressed the epinephrine induced ventricular premature complexes (VPCs) and TdP in humans as well [93]. Moreover, it was suggested that semotiadil inhibits Ca^{2+} release from Ca^{2+} stores or decrease the sensitivity of the contractile elements to Ca^{2+} on top of the $I_{Ca,L}$ inhibition [71].

Those CCAs, possessing large inhibitory actions on other ion channels, might have increased antiarrhythmic properties. The reduction of fast sodium current (I_{Na}) and/or Na^+/Ca^{2+} exchange current (I_{NCX}) (as with bepridil [94]) would reduce the risk of the development of triggered AP and the generation of afterdepolarizations, respectively.

In rats with vitamin D3 induced calcium overload, fantofarone decreased the calcium content in the thoracic aorta, mesenteric artery and also in their heart [95].

2. The inhomogeneity of the repolarization times exists even in the healthy myocardium. That includes the transmural dispersion of repolarization (TDR) [96], the apico-basal gradient in repolarization [97] as well as the different repolarization times in left versus right ventricular muscle [98]. The increase of these inhomogeneities can lead to reentry arrhythmias [90]; therefore the reduction of TDR might be another important mechanism by which the antiarrhythmic action of CCAs can be mediated. This was observed in case of verapamil in a feline model of acquired long QT syndrome (LQTS) [92] as well as in patients with congenital LQTS [93]. A parallel and homogeneous prolongation in repolarization and refractoriness were thought to be essential for the antiarrhythmic effect of bepridil [99].

3. The generation and propagation of action potentials (AP) in pacemaker tissues are largely mediated by L-type calcium channels. That is the reason why CCAs with low vascular selectivity (having remarkable action on myocardium as well) are very effective in supraventricular tachyarrhythmias (AF and atrial flutter (AFL)). Namely, these CCAs effectively reduce the atrioventricular (AV) conduction leading to a negative dromotropic effect. For a recent review on AF see ref [100].

4. Prolongation of the recovery from inactivation of calcium channels was described with verapamil [54], bepridil [35], semotiadil and also with diltiazem [39]. This alteration of channel behavior can also contribute to the antiarrhythmic action of CCAs by increasing the refractory period (RP) of nodal tissues. This mechanism, similarly to the negative dromotropic effect of CCAs can be especially useful against supraventricular tachyarrhythmias and lead to the reduction of the ventricular rate (VR).
5. The amplitude of systolic calcium transients depends on at least two factors. One of them is the amplitude of the trigger for the calcium release from the sarcoplasmic reticulum, namely the calcium influx through mainly the L-type calcium channels of the sarcolemma. The other one is the calcium content of the intracellular calcium stores not to mention the sarcoplasmic reticulum gain which relates the amount of released calcium to the amount of the triggering calcium [101],[102]. These two factors are both reduced by CCAs, therefore it is not surprising that CCAs lead to the decrease of calcium transient amplitudes (for verapamil and mibefradil [103] for D600 [104], for SR33805 [40], for KT-362 [105] and for AH-1058 [106]). The major ATP using process in myocytes is the contractile machinery, the activity of which depends on intracellular calcium. Therefore, the previously mentioned reduction of intracellular calcium level will reduce adenosine triphosphate (ATP) consumption. Similarly, the reduction of VR will lead to an energy sparing effect and a reduction in ATP usage. Arrhythmias can develop in ischemic myocardium in which the ATP levels drop, therefore the preservation of ATP by CCAs could be another reason of their antiarrhythmic action.
Myocardial oxygen consumption can be an indirect measure of the metabolic activity of the myocardium and therefore it is likely to be directly proportional with ATP requirement. CCAs reportedly reduce cardiac oxygen consumption (for verapamil [107], for fantofarone [108], for KT-362 [42] and for bepridil [109], [110]) therefore again leading to a possible antiarrhythmic action.
The mechanism how the reduction of intracellular ATP level can lead to arrhythmias can be related to the function of ATP dependent potassium channels [111].
6. CCAs exert useful hemodynamic actions including vasodilatation leading to reduced preload and afterload, respectively. These will reduce the work of the heart, causing again a potential ATP sparing effect. Moreover, the increase in coronary flow (CF) can be found with CCAs. This effect is often not homogenous but a redistribution of the available CF can be seen. In some cases, CF of the ischemic area is increased improving the myocardial oxygen supply/oxygen requirement ratio [112] which is again beneficial.
7. Many CCAs were shown to inhibit not only calcium channels but also other ion channels. Inhibitions of I_{Na} and I_{NCX} have already been mentioned above to reduce the calcium overload and its arrhythmogenic consequences. Sodium channel inhibition was observed with many CCAs although in most cases only indirect, maximal rate of depolarization (V_{max}) measurements are available (for verapamil [113], for diltiazem [114], for siratiazem [115], for semotiadil [116], for levosemotiadil [117], for KT-362 [118], for mibefradil [119], for AH-1058 [38] and for bepridil [33]).
Potassium channels were also reduced by some nonselective CCAs. The reduction of major repolarizing currents including transient outward potassium current (I_{to}), I_K and inward rectifier potassium current (I_{K1}) would lead to the prolongation of AP thereby an increase in the RP. BRL-32872 for instance inhibits I_{Kr} much more potently compared to $I_{Ca,L}$ [41]. The increase of the RP together with the reduction of several potassium currents were observed with bepridil (see later). The prolongation of the RP induced by many CCAs on the level of nodal tissues as well as atrial and ventricular myocardium will lead to antiarrhythmic action as reentry will occur less likely.
There are several reports about the inhibition of other potassium currents by some CCAs. Some of these are mostly expressed in the atrial muscle as acetylcholine-activated potassium current ($I_{K,Ach}$) and the ultrarapid component of delayed rectifier potassium current (I_{Kur}). The reduction of $I_{K,Ach}$ together with the increase in atrial effective refractory period (ERP) was reported with levosemotiadil [33], [117] and also with bepridil [120],[121]. The native current of I_{Kur} was blocked by verapamil in human atrial cells [122] and also by bepridil [33] and diltiazem [122] although in higher than therapeutic doses.
Bepridil blocked heterologously expressed sarcolemmal ATP dependent potassium channels, but the drug opened mitochondrial ATP dependent potassium channels which latter is believed to be cardioprotective [123]. Both levosemotiadil and semotiadil reduced ATP dependent potassium current ($I_{K,ATP}$) in high doses [124]. Interestingly, the infarct size reducing effect of mibefradil in isolated, Langendorff-perfused rat hearts [125] and in anesthetized pigs [126], [127] was attributed at least in part to its $I_{K,ATP}$ activating property.
Sodium activated potassium current ($I_{K,Na}$) was reduced by verapamil and levosemotiadil [127] as well as by bepridil, which was suggested to be responsible for the non reverse-rate dependent AP lengthening effect of bepridil [127].

7. Proarrhythmic actions of CCAs

Like other pharmacological antiarrhythmic intervention (particularly class III agents), some CCAs may also be proarrhythmic. The redistribution of CF is one of these unwanted actions. Verapamil caused a coronary steal from the ischemic area of the myocardium [128] thereby likely aggravated the reduction of oxygen supply, ATP production and levels. Coronary dilation itself, regardless of its position (ischemic or non-ischemic area of the myocardium), is not necessary beneficial especially if it occurs during reperfusion as it could amplify the risk of the development of reperfusion arrhythmias. Some CCAs including D600 was found to be arrhythmogenic as it induced a prolongation of the APD and provoked EADs in a special model of papillary muscles of guinea-pig hearts [129]. In Langendorff-perfused rabbit hearts D600 at higher doses when it also inhibits I_{Na} converted ventricular tachycardia (VT) to slow VF (11.9±2.3 Hz) [130]. Bepridil was also reported to evoke EAD at long cycle length (CL) in canine Purkinje fibers [131] and it also increased TDR by mainly lengthening M cell APD in canine wedge preparations [132]. Moreover, in vivo animal studies reported arrhythmogenic action of bepridil during coronary occlusion (but not during reperfusion) [133], [134]. VT, prolongation of QTc interval and TdP were detected with bepridil treatment in permanent AF patients, while no ventricular arrhythmias were seen with amiodarone [134]. Anipamil was also found arrhythmogenic at least in pentobarbitone-anesthetized pigs where it increased the occurrence of VT and VF [135], [136]. In rats with healed infarcts and ventricular dysfunction, 8-week-long anipamil treatment aggravated left ventricular dilatation and remodeling, thereby reduced survival [136].

Verapamil, together with other CCAs, is on the list of drugs to avoid in the treatment of Brugada syndrome due to their potential proarrhythmic action [137], [138]. Bepridil is an exception but due to its I_{to} and $I_{K,Ach}$ and certainly not its calcium channel blocking action [139]. CCAs should also be avoided in the treatment of short QT syndrome as in some genetic, congenital forms of the disease (SQT4 and 5) the calcium channels are already conduct a smaller current [140], [141]. Moreover, together with other drugs, verapamil is used to model early repolarization in animal studies [142]. However, verapamil was effective but unfortunately it did not prevent sudden death [143].

8. Additional electrophysiological effects of CCAs

8.1. Phenylalkylamines

Verapamil

Verapamil (**Fig. 2.**) is the best known phenylalkylamine which is used in antiarrhythmic treatment even today although it is not a new compound at all. Actually, it was probably the first CCA introduced to human clinical treatment. It was considered to be a coronary vasodilator therefore its use started as an antianginal agent in 1962 in Germany [144].

The therapeutic plasma concentration of free verapamil (not bound to proteins) in humans is between 20-800 nM [145], although the mean myocardial to plasma concentration ratio was approximately seven suggesting accumulation of the drug in the heart [146]. Indeed, verapamil can accumulate in canine myocardium in a chamber specific manner showing greater accumulation in the ventricles compared to the atria without having left versus right-sided specific distribution [147].

Apart from the calcium channel inhibition, verapamil is likely to inhibit sodium channels as V_{max}, which is often used as an indirect measure of I_{Na}, was reduced by the drug in supratherapeutic concentrations (IC_{50} of 10 μM) in guinea-pig [20]. In isolated canine Purkinje fibers 6 μM verapamil or above decreased V_{max}, AP amplitude (APA) and conduction velocity [148]. The most pronounced effect on V_{max} was observed in guinea-pig right ventricular muscle where 1 μM evoked 42 % reduction [113].

Potassium channels were also reduced by verapamil. In guinea-pig ventricular myocytes 1 and 5 μM verapamil reduced I_{Kr} by 50 and 87 %, respectively [149]. The slow component of the delayed rectifier potassium current (I_{Ks}) was recuced by 18 and 40 % in the presence of 1 and 5 μM verapamil, respectively [149]. Verapamil exerted an inhibitory action on expressed potassium channel proteins including human ether-a-go-go (hERG) channels in the possible therapeutic level in the myocardium [150], [151] and $K_v1.5$ (responsible for I_{Kur}) channels with an IC_{50} of 5.1 μM [151].The native current of I_{Kur} was also blocked by verapamil in human atrial cells from as low as 1 μM [122]. Verapamil blocked $I_{K,Na}$ in guinea-pig ventricular cells with an IC_{50} of 3.36 μM [127]. Verapamil reduced the open probability of large-conductance calcium-activated potassium channels (BK_{Ca}) in rat aortic myocytes with a dissociation constant of 4.1 μM. Results suggested an open channel block [152].

In guinea-pig cardiomyocytes the APD was reduced by 45 % in 10 μM verapamil, which also reduced the plateau of the AP [153]. In contrast, verapamil slightly increased APD in guinea-pig papillary muscle [154]. The APD increase

by verapamil was also seen in spontaneously beating rabbit SA nodal cells together with the reduction of V_{max} and APA [155].
The effects of verapamil in nodal tissues included an increase in CL, maximal diastolic potential (MDP) and APD but a reduction in both V_{max} and APA on rabbit SA node tissue [156].

D600 (gallopamil)

D600 (**Fig. 2.**) had a peak plasma concentration of 61-77 ng/ml (equivalent to approximately 120-150 nM) in patients taking 50 mg D600 three times a day for 28 days [157]. Myocardial concentrations could be even higher as, similarly to verapamil, D600 can be accumulated, at least in guinea-pig left auricles, to up to six times [158].

D600 is a methoxy derivative of verapamil which was also shown to reduce I_{Na}. In cultured chick heart cells I_{Na} was reduced by D600 with an IC_{50} of 30 μM [159]. 10 μM D600 had no effect on V_{max} in guinea-pig ventricular cells [20]. In contrast, the same study reported 50 % reduction by 10 μM verapamil suggesting a less potent I_{Na} inhibition by D600.

I_{to} of rat ventricular cardiomyocytes was reduced with an IC_{50} of 3 μM by D600 [160].
D600, at 1 and 10 μM, decreased the open probability of BK_{Ca} channels by 37 and 84 %, respectively, in rat aortic myocytes which was more potent compared to that of verapamil [152].

Tiapamil (Ro 11-1781)

Tiapamil (**Fig. 2.**), similarly to verapamil, inhibited calcium-induced contractions in rat renal artery, canine coronary artery and rabbit main pulmonary artery in a dose-dependent manner [161]. Sodium channel inhibition was suggested in guinea-pig papillary muscles where tiapamil reduced V_{max} at concentrations above 1 μM with an IC_{50} value of 70 μM in a use-dependent manner whereas verapamil was less potent [162] at least in that study. Similarly, tiapamil caused marked alterations of the normal sodium AP, namely the reduction of V_{max} and the prolongation of plateau phase [163].

Anipamil

Only indirect effects are available suggesting the calcium channel inhibitory action of anipamil (**Fig. 2.**) as the drug dose-dependently reduced the contractile force of Langendorff-perfused rat hearts with an IC_{50} of 100 nM. Comparison to the other phenylalkylamines is difficult as rat data are not available but anipamil was slightly less potent compared to D600 (IC_{50} of 60 nM in guinea-pig left auricles) and its negative inotropic action was the same as that of verapamil (IC_{50} of 100 nM in isolated guinea-pig left atria). Anipamil was found to be selective to cardiac muscle and had no effect on coronary smooth muscle up to 100 μM in isolated rabbit heart. In contrast, both verapamil and D600 reduced heart rate (HR) up to asystole and evoked coronary spasm together with their negative inotropic effect. The reduction in contractility was only partially reversible and long lasting (up to 12 hours) with anipamil in contrast to verapamil and D600 whose negative inotropic effect was completely reversible within 3 hours of washout [164].

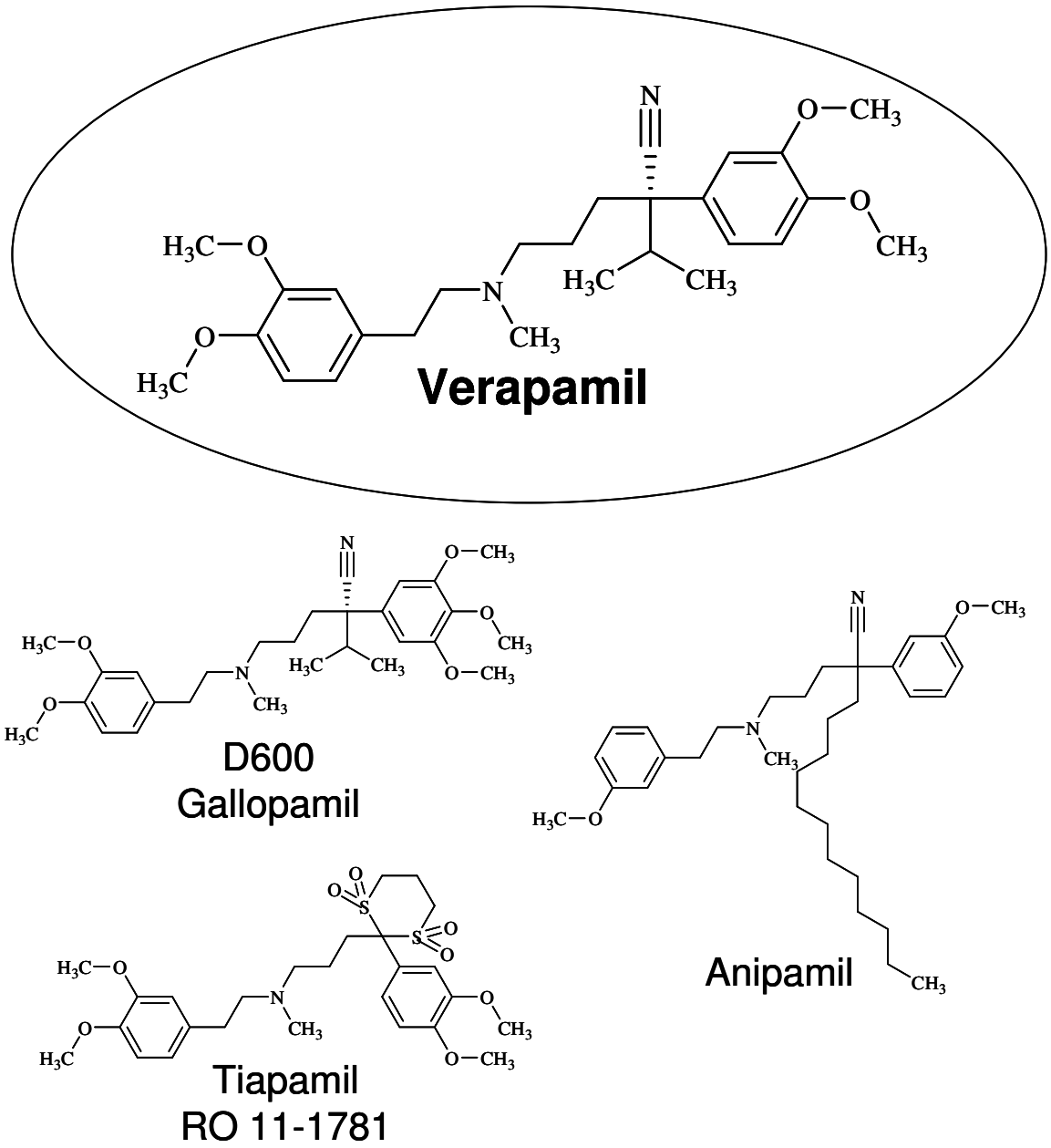


FIG. 2. Chemical structure and IUPAC name of phenylalkylamines. The first and best known one is the circled verapamil.

Verapamil, 2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-ylpentanenitrile

D600, 5-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]-2-propan-2-yl-2-(3,4,5-trimethoxyphenyl)pentanenitrile

Tiapamil, N-[2-(3,4-dimethoxyphenyl)ethyl]-3-[2-(3,4-dimethoxyphenyl)-1,1,3,3-tetraoxo-1,3-dithian-2-yl]-N-methylpropan-1-amine

Anipamil, 2-(3-methoxyphenyl)-2-[3-[2-(3-methoxyphenyl)ethyl-methylamino]propyl]tetradecanenitrile

8.2. Benzothiazepines

Diltiazem

Diltiazem (**Fig. 3.**) is the prototype of benzothiazepine structure type CCAs.

The human therapeutic plasma concentration of diltiazem is between 100-700 nM, but after correction to protein binding it was only 10-50 nM [145].

Diltiazem reduced I_{Kur} in human atrial myocytes in a dose-dependent manner with an IC_{50} of 11.2 μM, which was again less potent compared to that of verapamil (IC_{50} of 3.2 μM) [122], [165].

Glibenclamide-sensitive potassium currents in Xenopus oocytes were blocked by diltiazem in a stereoselective manner with IC_{50} values of 4.2, 13.3, 35.8 and 75.9 μM for (+)-trans, (-)-trans, (-)-cis and (+)-cis, respectively [124]. Interestingly, this order of blocking potency of the stereoisomers of diltiazem was exactly the opposite in case of $I_{Ca,L}$ inhibition.

9 μM IC_{50} value was reported for I_{Na} inhibition in guinea-pig ventricular cells, however, L-cis diltiazem was applied instead of the racemic molecule in that study [166]. Indirect measurements about the I_{Na} blocking action of diltiazem (V_{max} and sometimes APA determination of fast APs) are available in cat by 2.2 μM [114], in guinea-pig by 22 μM [167], in dogs by 11 μM [168] and also in human from 30 μM [169]. When compared to verapamil, diltiazem was again less potent in reducing V_{max} in canine Purkinje fibers and in guinea-pig ventricular muscle as well.

Regarding the effects of diltiazem on the duration of fast APs, one can find a slight increase in guinea-pig papillary muscles [154], increased APD_{80} in ferret right ventricular papillary muscles [25]; no change in rabbit ventricular APD up to 10 μM [170] and in feline right ventricular fibers by 2.2 μM diltiazem [114]; and also reduction of APD in guinea-pigs ventricular muscle [167], in canine Purkinje fibers [171] and in human ventricular myocardium [169] by 110, 1 and 10 μM diltiazem, respectively. The effect of diltiazem on early repolarization duration of the fast APs corresponding to the plateau phase (APD_{20} and APD_{30}) is equivocal in the literature as diltiazem reduced these values and depressed the plateau potentials in ferret right ventricular papillary muscles [25], canine ventricular muscles and Purkinje fibers [168].

Comparing diltiazem to verapamil, similar effects were found on AV nodal conduction time (CT) (greater increase during tachycardia compared to that during sinus rhythm (SR)) but the tau-on was shorter for diltiazem [172]. Similar actions were detected in canine ischemia induced VF with verapamil [173], [174].

Diltiazem was less effective compared to verapamil in most of their evoked actions. This was the case in reducing V_{max} in canine Purkinje fibers [148], [168] and in guinea-pig ventricular muscle [113], [167]; in reducing inotropy in dogs [175], [176] and in guinea-pig myocardial preparations [154]; in reducing chronotropy on rabbit SA node tissue [156], in anesthetized dogs [177] and in guinea-pig myocardial preparations [154]; in exerting vasorelaxing effect [154], [176]. Similar antiarrhythmic effect was observed with twice as large dose of diltiazem compared to verapamil in open-chest anesthetized dogs [178].

In contrast to the previously mentioned results, the negative chronotropic action of diltiazem was more potent than that of verapamil in anesthetized dogs [177] and in canine right atrium [175]. The vascular selectivity of verapamil was slightly lower compared to that of diltiazem [176].

Siratiazem (LR-A113)

Siratiazem (**Fig. 3.**) was designed to be resistant to N-demethylation and had 1.6-1.9 times longer half-life in conscious rats after both oral and intravenous administration without a major increase in its bioavailability [179]. In depolarized ovine coronary artery rings potassium-stimulated calcium uptake was also inhibited by siratiazem and diltiazem with similar potencies [30]. Siratiazem dose-dependently (1-10 μM) reduced APA, V_{max}, APD_{50} and APD_{90} values of ovine Purkinje fibers without affecting resting membrane potential (RMP) [115].

Clentiazem (TA-3090)

Clentiazem (**Fig. 3.**) is a chloride containing diltiazem derivative having peak plasma levels of 17 and 19 ng/ml (approximately 30-33 nM) in patients with essential hypertension [180]. Clentiazem antagonized contractions of rabbit myocardium with the same potency compared to diltiazem (IC_{50} values of 43 and 39 μM, respectively) but in a longer-lasting manner [28]. On isolated human right ventricular trabeculae clentiazem evoked negative inotropic actions with an EC_{50} of 8.8 μM which was similar to that of diltiazem (7.2 μM EC_{50}) [27]. On isolated rabbit tissues clentiazem was more vasoselective than diltiazem [28]. Clentiazem proved to be more effective than diltiazem but less potent than verapamil in reducing the spontaneous rate of rabbit SA nodal tissue. Clentiazem reduced V_{max} and APA while increased MDP and APD and the magnitude of these effects was again intermediate compared to diltiazem (being the least potent) and verapamil (being the most potent) [156]. In vitro experiment on rabbit hearts showed that, similarly to diltiazem, clentiazem (10-1000 nM) caused a dose-dependent

increase in AH interval without affecting HV interval. In AV and SA nodal cells 1 μM clentiazem reduced APA, V_{max}, APD_{50}, APD_{20} and MDP without changing APD_{90}. In AV node the drug prolonged ERP and up to 10 μM it did not change ventricular AP [170]. In dogs, sustained negative chronotropic effects were recorded in high dose and these were correlated well with myocardial clentiazem levels [181].
Similarly, clentiazem was more potent in lowering mean arterial pressure (MAP) without evoking a positive reflex chronotropic action in dogs compared to diltiazem [182]. Clentiazem increased coronary blood flow just as diltiazem [183] but its effect was more prolonged [184] and showed higher selectivity for coronary arteries [183].

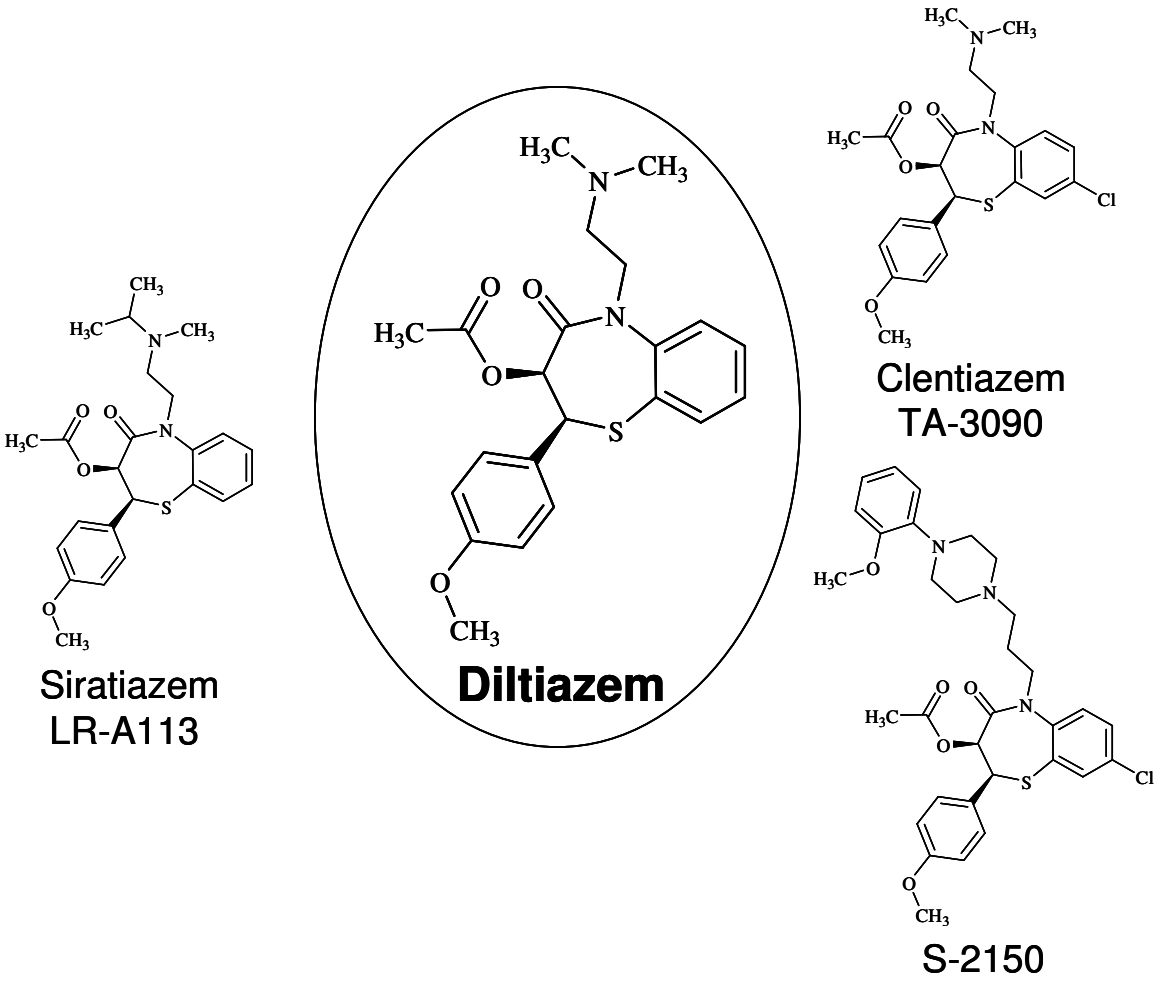


FIG. 3. Chemical structure and IUPAC name of benzothiazepines. The first and best known one is the circled diltiazem.
Diltiazem, [(2S,3S)-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate
Clentiazem, [(2S,3S)-8-chloro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate
Siratiazem, [(2S,3S)-2-(4-methoxyphenyl)-5-[2-[methyl(propan-2-yl)amino]ethyl]-4-oxo-2,3-dihydro-1,5-benzothiazepin-3-yl] acetate
S-2150, Acetic acid 8-chloro-2-(4-methoxy-phenyl)-5-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propyl}-4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepin-3-yl ester

8.3. Other CCAs

Semotiadil (SD-3211)

Semotiadil (**Fig. 4.**) blocked glibenclamide-sensitive potassium current in Xenopus oocytes more potently compared to verapamil (IC_{50} values of 10 and 60 μM, respectively) [124].

Semotiadil, but not diltiazem, inhibited the norepinephrine-induced transient contraction, even in the absence of external Ca^{2+} and in nifedipine-treated muscles, suggesting an inhibition of Ca^{2+} release from Ca^{2+} stores or decrease in sensitivity of the contractile elements to Ca^{2+} on top of the $I_{Ca,L}$ inhibition [71].

Semotiadil (1-10 μM) reduced APD in a dose-dependent manner without affecting the RMP or V_{max} in guinea-pig papillary muscles. The V_{max} of slow responses was inhibited only above 1 μM [116].

Semotiadil exerted potent inhibition on both depolarization-induced (evoked by KCl) and ligand-induced (histamine and norepinephrine) contractions in porcine coronary arteries [6], in isolated rat aortas [71] and also in isolated canine coronary arteries [185]. The inhibition of potassium-induced contractions was usually more potent compared to both diltiazem and verapamil.

Levosemotiadil (SD-3212)

Levosemotiadil (**Fig. 4.**) is the stereoisomer of semotiadil with an approximate plasma level of 350 nM [117]. Levosemotiadil inhibited $I_{Ca,L}$ and I_{Na} in a dose-dependent manner with IC_{50} values of 1.3 and 3.9 μM, respectively, in guinea-pig atrial cells. The steady-state inactivation curves of both currents were shifted to more negative potentials by 1 μM levosemotiadil [33]. V_{max} inhibition by levosemotiadil was described in guinea-pig right ventricular papillary muscles (3 μM and above in a use-dependent manner) [186], in canine tissue (0.3-3 μM in a use- and concentration-dependent manner) [117] and in rabbit papillary muscles (3-10 μM in a use- and concentration-dependent manner) [187].

Levosemotiadil blocks $I_{K,Na}$ in guinea-pig ventricular cells with an IC_{50} of 0.53 μM [127]. Glibenclamide-sensitive potassium channels ($I_{K,ATP}$) in Xenopus oocytes were blocked slightly more potently by levosemotiadil compared to semotiadil (IC_{50} values of 9 and 11 μM, respectively) [124].

$I_{K,Ach}$ was potently inhibited with an IC_{50} of approximately 0.29 μM. Carbachol induced AP shortening was reversed by 0.1-1 μM levosemotiadil in a dose-dependent manner in guinea-pig atrial cells [33].

Levosemotiadil significantly increased APD in canine tissue (1-3 μM) [117] and in rabbits (endocardial monophasic AP and in papillary muscles in the range of 3-10 μM) [187]. The prolongation of AP did not vary with stimulation frequency and levosemotiadil did not influence APA or RMP [187]. Similarly, levosemotiadil increased right atrial ERP with the same extent regardless of the CL [117].

Levosemotiadil (1-10 μM) evoked similar actions seen with semotiadil but not with diltiazem, suggesting an inhibition of Ca^{2+} release from Ca^{2+} stores or decrease in sensitivity of the contractile elements to Ca^{2+} [71].

SR 33805

SR 33805 (**Fig. 4.**) inhibited the high potassium depolarization-induced, sustained increases in intracellular calcium level and force with IC_{50} values of 3.2 and 49.4 nM, respectively [188]. It also sensitized myofilaments to calcium as in the medial strip of the porcine coronary artery SR33805 caused a leftward shift of both the intracellular calcium level-force and the intracellular calcium level-myosin light chain phosphorylation curves [188]. Similarly, 1-10 μM SR33805 induced the sensitization of the myofilaments to calcium in ventricular myocytes from both normal [40] and from end-stage heart failure (HF) rat hearts [189] without increasing the calcium transient amplitude. SR33805-induced sensitization of myofilament activation was found to be associated with a slight increase in myosin light chain-2 phosphorylation and a more significant decrease on troponin I phosphorylation, which latter was related to inhibition of protein kinase A activity by SR33805 [189]. SR33805 reduced APD and the amplitude of the calcium transient in rat ventricular myocytes. 10 nM SR33805 enhanced the amplitude of unloaded cell shortening and facilitated its relaxation. Moreover, it induced a significant increase in maximal calcium-activated force [40].

BRL-32872

BRL-32872 (**Fig. 4.**) inhibited I_{Kr} and $I_{Ca,L}$ with IC_{50} values of 0.028 and 2.8 μM, respectively, but had a limited effect on I_{K1} in isolated guinea-pig myocytes [41]. BRL-32872 evoked an unusual effect on APD. AP prolongation with 0.3-10 μM BRL-32872 had a bell-shape with the largest prolongation of 24-25 % occurring at 1 μM in both guinea-pig papillary muscle [41] and in canine Purkinje fibers [190]. Moreover, in guinea-pig papillary muscle the extent of prolongation did not depend on stimulation CL and no reverse-rate dependence was found [41].

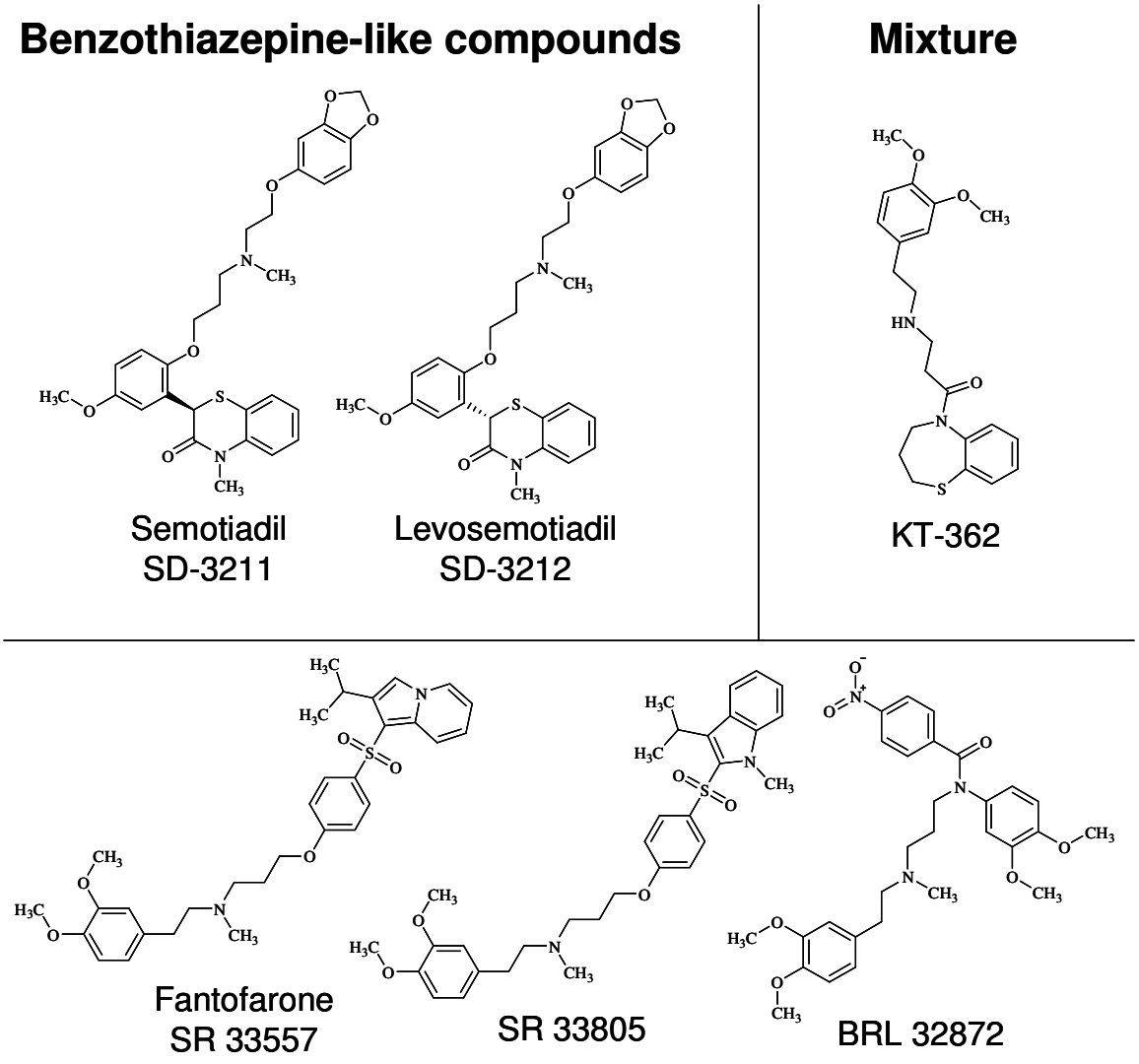


FIG. 4. Chemical structures and IUPAC names of benzothiazepine- (above) or phenylalkylamine-like (below) compounds and one with similarity to both (up right).

Semotiadil, (2R)-2-[2-[3-[2-(1,3-benzodioxol-5-yloxy)ethyl-methylamino]propoxy]-5-methoxyphenyl]-4-methyl-1,4-benzothiazin-3-one

Levosemotiadil, 2-[2-[3-[2-(1,3-benzodioxol-5-yloxy)ethyl-methylamino]propoxy]-5-methoxyphenyl]-4-methyl-1,4-benzothiazin-3-one

KT-362, 1-(3,4-dihydro-2H-1,5-benzothiazepin-5-yl)-3-[2-(3,4-dimethoxyphenyl)ethylamino]propan-1-one

Fantofarone, N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-3-[4-(2-propan-2-ylindolizin-1-yl)sulfonylphenoxy]propan-1-amine

SR 33805, [2-(3,4-Dimethoxy-phenyl)-ethyl]-{3-[4-(3-isopropyl-1-methyl-1H-indole-2-sulfonyl)-phenoxy]-propyl}-methyl-amine

BRL 32872, N-(3,4-dimethoxyphenyl)-N-[3-[2-(3,4-dimethoxyphenyl)ethyl-methylamino]propyl]-4-nitrobenzamide

KT-362

In isolated papillary muscles of guinea-pig 3-30 μM KT-362 (**Fig. 4.**) caused a dose- and use-dependent decrease in V_{max} without changing RMP, suggesting the inhibition of I_{Na}.

KT-362 (1-30 μM) decreased both systolic and diastolic intracellular calcium concentration in a dose- and use-dependent manner in cultured neonatal rat ventricular cells aggregates. 30 μM KT-362 increased time to peak of the Ca^{2+} transient, while the half-life of the calcium transient was prolonged at 10 μM and above. These effects of KT-

362 on Ca^{2+} transients could be mimicked by simultaneous application of 1 µM D600 and 10 µM ryanodine, suggesting that KT-362 inhibits both sarcolemmal calcium channels and calcium release channels of the sarcoplasmic reticulum [105]. Other studies also support the inhibition of calcium release channels of the endoplasmic reticulum (inositol-triphosphate receptor) by KT-362 in the micromolar range in rabbit aorta [191] and in canine femoral arteries [192].

Mibefradil (RO 40-5967)

The therapeutic plasma concentration of mibefradil (**Fig. 5.**) was in the range of 10-1000 ng/ml (approximately 0.02-2 µM) [193].

Not only calcium channels were blocked by mibefradil as in CHO cells transfected with human $K_v1.5$ mibefradil showed a dose-, use- and voltage-dependent inhibition with an IC_{50} of 0.78 µM. Recovery from inactivation was faster with mibefradil [194]. Mibefradil inhibited the expressed hERG and K_vLQT1/IsK channel currents with IC_{50} values of 1.43 and 11.8 µM, respectively [150]. Mibefradil blocked the delayed rectifier potassium current, the hERG potassium current and I_{K1} with IC_{50} values of 0.3, 0.7 and 5.6 µM, respectively, in human myoblasts [195]. $Na_v1.5$, the cardiac isoform of sodium channels expressed in HEK cells, was blocked by mibefradil with an IC_{50} value of 1 µM [119] and with IC_{50} values of 0.5 and 2.9 µM from holding potentials of -100 and -130 mV, respectively [196]. In murine B cell lines mibefradil blocked voltage-gated potassium current and large-conductance background potassium current with IC_{50} values of 1.9 and 2.3 µM, respectively. Interestingly, calcium-activated potassium current was increased by 0.5-5 µM mibefradil as the drug increased both calcium sensitivity and maximal activity of these channels. At high concentrations (>10 µM), mibefradil inhibited calcium-activated potassium channel current in a voltage-dependent manner [197].

Several studies described the effects of mibefradil on APs. 100 nM mibefradil reduced APA and AP firing rate (sometimes even stopped the activity) as well as shifted MDP to more positive potentials in rabbit SA node cells [51]. In 10 µM it reduced V_{max} and phase 4 slope, without affecting APD [48]. The effect of mibefradil on APD is variable. No effect was detected in human atrial myocytes in 1-10 µM [153] and in 0.1-1 µM on monophasic APDs in Langendorff-perfused rabbit heart [153]. Reduction of APD was observed in guinea-pig ventricular cells in 10 µM [153]. In contrast, mibefradil (3-10 µM) increased APD in canine Purkinje fibers [52]. The reduction of the plateau of the AP was described by 1 and 10 µM mibefradil in isolated guinea-pig ventricular cardiomyocytes and in human atrial myocytes [153]. Same was seen in canine Purkinje fibers by doses of 3-10 µM [52]. Indicating the inhibition of I_{Na}, 10 µM mibefradil reduced overshoot potential and APA in isolated guinea-pig cardiomyocytes but had no effect on the RMP [153].

Bepridil (CERM-1978)

The therapeutic plasma concentration of bepridil (**Fig. 5.**) is approx. 2 µM [198] although the unbound concentration of bepridil is much lower, approximately 15 nM [199]. Oral doses of 200, 300 and 600 mg/day bepridil given to volunteers resulted in the peak plasma levels of 0.28, 0.44 and 0.97 µg/ml (0.76, 1.2 and 2.6 µM), respectively [200].

10-100 µM bepridil evoked calcium sensitizing action and increased force and ATPase activity in skinned porcine trabeculae [201]. In cultured neonatal rat ventricular cells 10 µM bepridil sensitized myofilaments to calcium [104]. 1 µM bepridil reduced oxidative phosphorylation in rabbit heart mitochondria by 50 % [202].

I_{Na} was also reduced by bepridil in neonatal rat cells with an IC_{50} of 30 µM (much less potently compared to $I_{Ca,L}$ inhibition). I_{Na} steady-state inactivation was shifted to more negative potentials and recovery from inactivation was slowed down just as with $I_{Ca,L}$ [35]. In guinea-pig ventricular cells I_{Na} inhibition by bepridil was more potent as the IC_{50} was 20 µM [203]. I_{Na} in guinea-pig atrial cells was even more sensitive to bepridil (IC_{50} of 4.34 µM) which is similar to that seen by levosemotiadil [33]. Interestingly, when 10 µM bepridil was applied for 24 h on isolated neonatal rat cardiomyocytes it augmented I_{Na} with 50 % by inhibition of calmodulin action leading to a decreased degradation of the $Na_v1.5$ α subunit while the same dose applied for 3 min reduced I_{Na} by 20 % [204].

Sodium/calcium exchange was reduced by only supratherapeutic bepridil doses (IC_{50} of 30 µM) in cardiac sarcolemmal membrane vesicles and bepridil acted mode-dependently as the calcium extrusion (forward mode) was inhibited more effectively [205]. In guinea-pig ventricular cells I_{NCX} was more sensitive to bepridil (IC_{50} of 8.1 µM) [94].

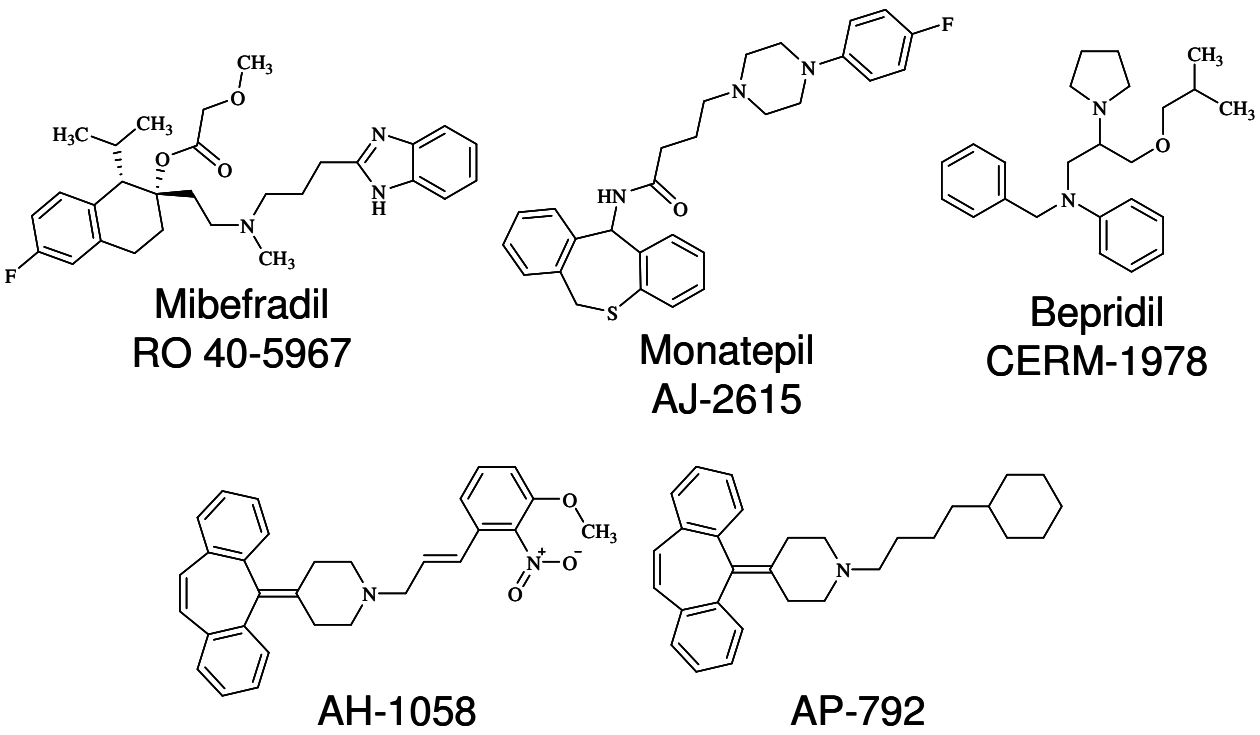


FIG. 5. Chemical structures and IUPAC names of various compounds with calcium channel antagonist action.
Mibefradil, [(1S,2S)-2-[2-[3-(1H-benzimidazol-2-yl)propyl-methylamino]ethyl]-6-fluoro-1-propan-2-yl-3,4-dihydro-1H-naphthalen-2-yl] 2-methoxyacetate
Monatepil, N-(6,11-dihydrobenzo[c][1]benzothiepin-11-yl)-4-[4-(4-fluorophenyl)piperazin-1-yl]butanamide
Bepridil, N-benzyl-N-[3-(2-methylpropoxy)-2-pyrrolidin-1-ylpropyl]aniline
AH-1058, 4-Dibenzo[a,d]cyclohepten-5-ylidene-1-[3-(3-methoxy-2-nitro-phenyl)-allyl]-piperidine
AP-792, 1-(4-Cyclohexyl-butyl)-4-dibenzo[a,d]cyclohepten-5-ylidene-piperidine

HCN4 channels (underlying "funny" pacemaker current) expressed in HEK cells were also blocked by bepridil with an IC_{50} of 4.9 μM whereas verapamil was much less potent inhibitor of those channels (IC_{50} of 45 μM) [206]. 10 μM bepridil reduced "funny" pacemaker current in rabbit sinus node cells [207].
Regarding potassium currents, bepridil influenced all major cardiac potassium currents. Atrial potassium currents, like the current of expressed hK_v1.5 channels (I_{Kur}) in HEK cells and $I_{K,Ach}$ in guinea-pig atrial cells were inhibited with IC_{50} values of about 7 and approximately 0.75 μM, respectively [33], [208]. The inhibition of $I_{K,Ach}$ by bepridil was less potent compared to that of levosemotiadil (IC_{50} of 0.3 μM). The carbachol-induced AP shortening was reversed by levosemotiadil more potently compared to bepridil [33].
Similarly to what was observed with I_{Na}, long-term bepridil treatment (12 h, between 0.3-30 μM) increased the protein level of K_v1.5 channels in a concentration-dependent manner with an IC_{50} of 1 μM by delaying the degradation process of K_v1.5 channel proteins acting at the endoplasmic reticulum as a chemical chaperone. The K_v1.5 current measured as 4-AP sensitive current was increased by 3 μM bepridil to 300 % of control [209].
10 μM bepridil completely blocked K_{ir}6.2+SUR2A channels (underlying $I_{K,ATP}$) expressed in HEK 293 cells, but the drug opened mitochondrial K_{ATP} channels thereby promoted cardioprotective action [123]. In follicle-enclosed Xenopus oocytes $I_{K,ATP}$ was blocked by bepridil with an IC_{50} of 7.6 μM, more effectively compared to verapamil (IC_{50} of 60 μM) but to the same extent as with levosemotiadil and semotiadil (IC_{50} values of 9 and 11 μM, respectively [124]. $I_{K,Na}$ in guinea-pig ventricular cells was reduced by bepridil with an IC_{50} of 0.51 μM, which can be the reason of the non reverse-rate dependent AP lengthening effect of the drug [127].
In guinea-pig ventricular myocytes 1-20 μM bepridil increased APD due to inhibition of I_K and I_{K1} [210] but others found that neither I_K nor I_{K1} was sensitive to bepridil up to 100 μM [35]. In sheep Purkinje fibers I_K, I_{K1} and I_{to} was reduced by bepridil to various extent. Outward I_{K1} was reduced by 30 % in 1.8 μM bepridil, I_{to} was reduced with an IC_{50} of 2.5 μM and I_K was also reduced by 10 μM [211]. In contrast, 10 μM bepridil had no effect on I_K in rabbit sinus node cells [207]. In HEK cells expressing KCNQ1 and KCNE1 channel proteins (underlying I_{Ks}) bepridil

reduced the current with IC_{50} of 5.3 and 2.5 μM when 250 and 1000 ms long depolarizing pulses were applied, respectively. This suggests a greater affinity of binding to the closed channel [212]. Others found an IC_{50} of 10 μM for expressed K_vLQT1/IsK channels mediated currents in COS cells [150]. Native I_{Ks} in guinea-pig ventricular cells was blocked by bepridil with an IC_{50} of 6.2 μM [213]. hERG channels expressed in HEK cells were blocked by bepridil with an IC_{50} of 26 nM [44] whereas in COS cells the IC_{50} value was 0.55 μM [150]. Native I_{Kr} currents in guinea-pig ventricular cells were reduced with an IC_{50} of 13.2 μM [213], less potently as expressed hERG protein. Moreover, it was suggested that bepridil can also inhibit $I_{K,Ach}$ [120].

AH-1058

In isolated guinea-pig cardiomyocytes AH-1058 (**Fig. 5.**) dose-dependently reduced the amplitude of the calcium transient [106] and 10 μM AH-1058 blocked I_{Na} by 15 % without reducing I_{Kr}, I_{Ks} or I_{K1}. In coronary-perfused right ventricular guinea-pig tissue preparations 10 μM AH-1058 shortened the APD with little effect on the RMP, V_{max} and overshoot potential. Contractile force was reduced by 0.1-10 μM AH-1058 in a dose-dependent manner [106].

9. Antiarrhythmic actions of certain CCAs

Out of the compounds discussed in this review only three (verapamil, diltiazem and bepridil) have a licence for medical use according to the U.S. Food and Drug Administration and only 9 of them was tested in medical treatment in human volunteers and/or patients (see Tables 4-6 below for a summary).

9.1. Phenylalkylamines

Verapamil

Animal studies with verapamil

The antiarrhythmic effect of verapamil was observed in various animal models including guinea-pig [172], rabbit [214], cat [92], pig [135], [215] and dog [174], [178]. Verapamil was more useful during ischemia than reperfusion in a canine study [133].

Clinical evidence for the antiarrhythmic actions of verapamil

Verapamil was effective in various cardiac arrhythmias including AF and paroxysmal supraventricular tachycardia (PSVT). In a study of 181 patients verapamil treatment (10 mg iv. over 15-30 seconds) significantly slowed sinus tachycardia, converted PSVT to SR and reduced VR in patients with AF and AFL very effectively [216]. It was also effective in Wolff-Parkinson-White (WPW) syndrome and AV junctional tachycardias but it was without effect in VT [217]. In acute myocardial infarction (AMI) patients with supraventricular tachyarrhythmia verapamil treatment reduced VR below 100 beats/min in every patients, but conversion to SR was achieved in only 1 out of 8 patients with AF and 7 out of 8 patients with AFL [218]. In 30 patients with PSVT, conversion to SR was achieved in 14 out of 29 patients by low-dose verapamil (0.075 mg/kg body weight), while in 9 out of 15 high-dose verapamil (0.15 mg/kg body weight) was required for the conversion [144].

Comparisons to β adrenergic receptor blockers showed superiority of verapamil in restoring SR for instance in patients with PSVT compared to practolol [219]. Verapamil, unlike atenolol, did not impair exercise tolerance but reduced HR in an equally potent manner during the treatment of chronic AF in digitalized patients [220]. There is a controversy regarding the superiority of verapamil over digoxin in the treatment of chronic, persistent or permanent AF as two studies reported that verapamil either alone or in combination with digoxin is a better choice compared to digoxin alone [221], [222] while others reached the conclusion that verapamil is not superior to digoxin treatment [223].It seems that verapamil is at least as effective as adenosine in terminating acute episodes of PSVT but it acts more rapidly [224]. According to another study one of the first choices for short-term medications of supraventricular tachycardia (SVT) is intravenously applied verapamil especially if adenosine is contraindicated or if the PSVT terminates rapidly but is immediately recurrent [225]. Two other recent studies concluded that the two drugs have similar efficacy in treating PSVT [226], [227]. Adenosine treatment had a higher rate of minor but unpleasant adverse effects and a greater risk of relapse, while some patients treated with verapamil may develop significant hypotension. Although 80 mg/day verapamil was effective in supraventricular tachyarrhythmias, it did not improve either exercise tolerance or cardiac output (CO) in 6 patients with chronic AF [228]. In contrast, in 18 patients with chronic AF verapamil (240 mg/day) proved to be effective in rate control and exerted a modest improvement in exercise tolerance [229]. The atrial ERP was reduced after AF and this reduction was prevented by verapamil but not procainamide treatment in adult patients without structural heart disease. During determinations of

the post-AF ERP, secondary episodes of AF were unintentionally induced in 12 % of verapamil patients compared to 90 and 80 % of saline and procainamide patients, respectively [230]. Similarly, atrial ERP shortening induced by pacing-induced AF was attenuated after verapamil infusion in 60 patients and the incidence and duration of secondary AF was also reduced [231].
As mentioned above, verapamil treatment successfully converted SVTs in all 10 patients having WPW syndrome [217] or AV reentrant tachycardia [232]. In contrast, verapamil had no effect in WPW syndrome in other studies [233], [234]. Verapamil was also effective in intractable ventricular arrhythmias refractory to other treatment in cases after cardiopulmonary bypass with normal cardiac function [235] and in severe rheumatic aortic regurgitation associated with a dilated, poorly contracting left ventricle [236] as well as in patients with obstructive hypertrophic cardiomyopathy [237]. Moreover, a low number of asymptomatic patients with recurrent, sustained VT and a pattern of right bundle branch block (RBBB) without organic heart disease VT could be both induced and terminated with electrical stimulation. Verapamil terminated VT and prevented the induction of sustained VT [238]. Similarly, in 19 patients the broad complex tachycardia demonstrating RBBB was converted to SR with verapamil (5 mg intravenous boluses of verapamil up to 20 mg or 20 mg verapamil infused over 20 min, titrated to effect with infusion stopped on conversion to SR) in 18 patients [239]. In 42 patients with idiopathic VT of left bundle branch block-like morphology verapamil treatment (120 mg 3 times daily) reduced VT in approximately 2/3 of the patients but some patients exhibit exacerbation of the arrhythmia and verapamil should be avoided [240]. Verapamil (5 to 20 mg intravenously over 60 s) effectively terminated paroxysmal sustained monomorphic VT, repetitive non-sustained VT or premature ventricular contractions in all 7 patients [241]. On the long run (a mean 5.8 year follow up) in 37 patients with sustained left VT without apparent structural heart disease verapamil (160 to 320 mg/day) proved to be the drug of choice for alleviating symptoms, but non pharmacologic therapy was necessary in 6 patients [242]. 5 mg verapamil injection terminated epinephrine induced VPCs and EADs [243] as well as in 8 patients with congenital LQTS verapamil eliminated or reduced EADs, suppressed the epinephrine induced VPCs and TdP. It also shortened AP and decreased TDR [93]. 6 patients with molecularly defined catecholaminergic polymorphic VT, all carrying a cardiac ryanodine receptor (RyR2) mutation and on β adrenergic receptor blocker therapy, received intravenous injection of 0.2 mg/kg verapamil and this reduced the number of isolated and successive premature ventricular complexes during exercise by 76 % and delayed the appearance of premature ventricular complexes [244]. In a small study done on 5 patients with either catecholaminergic polymorphic VT or polymorphic VT addition of verapamil to the β adrenergic receptor blockers reduced the number of ventricular ectopic beats during the whole exercise test as well as the ratio of ventricular ectopic to sinus beats in one patient [245]. Ischemia-induced arrhythmias were also effectively reduced by verapamil. In 31 patients (6 premature ventricular contractions, 19 accelerated idioventricular rhythms, 3 VTs, 2 VFs and 1 TdP all with a diagnosis of AMI after mechanical revascularization therapy within 6 h of onset of symptoms) intracoronary verapamil (0.25 to 1.0 mg) was effective in rapidly terminating all reperfusion-induced arrhythmias except for VFs. The intracoronary use of verapamil was without major complications and resumptions of arrhythmias [246].
Right ventricular outflow tract tachycardia as well as idiopathic verapamil sensitive ventricular tachycardia can both be treated with verapamil [247], [248]. In the former case verapamil works by reducing Ca^{2+} overload [249] while it slows down conduction and prevents re-entry in the latter [250].

D600 (gallopamil)
Animal studies with D600

In open-chest anesthetized dogs D600 significantly elevated myocardial blood flow in the non-ischemic area, but did not influence blood flow in the ischemic region [251] in contrast to the effect of verapamil, which either increased CF to the ischemic area [112] or caused a coronary steal from the ischemic area of the myocardium [128].
Ischemia and reperfusion-induced arrhythmias were reduced by D600 in rats [252], dogs [253] and guinea-pigs [254].

D600, in a dose reducing the contractile force by 50 %, induced a further prolongation of the APD and provoked EADs thus it had *arrhythmogenic* action in a special model of papillary muscles of guinea-pig hearts [129]. In Langendorff-perfused rabbit hearts 0.5 mg/l D600 infused during fast VF (dominant frequency, 19.1±1.8 Hz) consistently converted fast VF to VT. However, increasing D600, in a higher dose of 2.5 or 5.0 mg/l, converted VT to slow VF (11.9±2.3 Hz). D600 in the lower dose inhibited calcium current and mediated antiarrhythmic action. On the contrary, higher doses of D600 (evoking I_{Na} inhibition) can be *arrhythmogenic* [130].

In cats with left ventricular hypertrophy D600 prolonged sinus CL and AV CT but it did not protect against ventricular arrhythmia [255].

In open-chest anesthetized dogs with 20 min transient coronary artery occlusion D600 (0.13 mg/kg iv), similarly to verapamil (0.25 mg/kg iv) both given 5 min prior the ischemia reduced the epicardial conduction delay

of the ischemic area and almost completely suppressed ventricular arrhythmias and VF. Delayed ventricular reperfusion arrhythmias were also significantly reduced by both drugs [178]. In dogs 3-7 days after ligation of the left anterior descending coronary artery (LAD) D600 and verapamil (0.2-0.5 mg/kg iv) improved the conduction in reentrant pathways with abolition of both spontaneous and premature depolarizations evoked reentrant ventricular arrhythmias [256]. It seems that lower D600 doses were required to induce antiarrhythmic action in dogs therefore, D600 is likely to be more effective in the prevention of cardiac arrhythmias compared to verapamil. On the other hand it must be highlighted that D600 was *arrhythmogenic* at least in guinea-pigs and rabbits under certain conditions.

Clinical evidence for the antiarrhythmic actions of D600

Regarding human data, D600 significantly prolonged CT and the ERP of the AV node just as did verapamil [257]. Similarly, in 13 patients with normal SR intravenous administration of D600 increased AV CT. Second degree AV block occurred at lower stimulation rates in all patients during atrial stimulation but D600 had no effect on the impulse propagation in atrial tissue and within the His-Purkinje system [258]. In 10 AF patients, 100 mg orally given D600 decreased the HR for 10 hours. In 5 patients a regularization of the ventricular response was observed without bradycardia. Oral administration of 3 times 50 mg D600 daily decreased HR after a treatment period of 1 week to about 79 % of control [259]. D600, just as verapamil, evoked bradycardia or SA and AV nodal conduction disturbances. Gastrointestinal side effects were stomach problems after D600 and constipation after verapamil [260]. In 36 healthy men plasma digoxin concentration was increased by 16 % after 50 mg D600 three times a day and by 70 % after 80 or 120 mg verapamil [261]. Slow-release formulations of D600 (100 mg twice a day) and verapamil (120 mg twice a day) reduced peak HRs recorded during a 6-min walking test to a similar extent in 18 patients with permanent AF receiving oral digoxin without organic heart disease. D600 appeared to be less effective at controlling VR both at resting and during exercise [262].

Tiapamil (Ro 11-1781)

Animal studies with tiapamil

The antiarrhythmic actions of tiapamil were documented in open-chest pigs with LAD ligation. Tiapamil (6 mg/kg intravenously) decreased the incidence of VF by 60 %, maintained left ventricular maximal rate of pressure rise (dP/dt_{max}) after ligation and increased blood flow in the peripheral ischemic zone as well as in the peri-ischemic and non-ischemic zones [215]. In the same model verapamil in ten times lower dose fully prevented the occurrence of VF but left ventricular dP/dt_{max} was reduced to 50 % without changing blood flow in the peripheral, peri-ischemic, or non-ischemic zones.

Tiapamil reduced the incidence of ventricular ectopic beats (VEBs) both during LAD occlusion and reperfusion in a canine model [263]. Furthermore, tiapamil (4.75mg/kg) reduced myocardial infarct size which effect was lost with 11.25 mg/kg tiapamil probably due to marked hypotension and varying degrees of heart block [263]. In other studies tiapamil possessed again antiarrhythmic actions both during ischemia and reperfusion [264] but in others it proved effective against VF only during sympathetic stimulation and myocardial ischemia but not during reperfusion [173], [265].

In anesthetized open-chest dogs, intravenous tiapamil increased CF and decreased coronary vascular resistance, HR, blood pressure (BP) and total peripheral resistance. Tiapamil, in contrast to verapamil, did not depress myocardial contractility over a rather wide dose range and was more effective in increasing CF. Tiapamil dilated small but not large coronary arteries and raised pO_2 relatively more in the subendocardial than in the subepicardial layers of the myocardium [266].

Compared to verapamil, tiapamil was 33 and 18 times less potent in reducing the contractility of rabbit left atrium and right ventricular papillary, respectively [267]. Both tiapamil and verapamil decreased HR and increased CF in isolated cat hearts. The vascular selectivity of tiapamil was higher compared to verapamil [161].

Clinical evidence for the antiarrhythmic actions of tiapamil

In patients with AFL, AF or PSVT 1 mg/kg intravenous tiapamil produced a marked decrease in VR and conversion to SR was achieved in some cases [268]. Tiapamil was also effective in patients with chronic AF. AV CT was increased and the frequency of atrial ectopic beats was reduced. Moreover, ectopic beats were reduced by 30-50 % in 6 out of 20 cases in patients with ventricular premature beats previously not responding to antiarrhythmic therapy [269]. In a small study tiapamil effectively restored SR and prevented tachycardias in patients with recurrent PSVT except in those with retrograde conduction involving an accessory pathway [270]. Tiapamil was also without effect in WPW syndrome patients on anterograde or retrograde RPs of the accessory pathway or on that of the

ventricle [271]. Tiapamil (3 times 200 mg per os daily) had positive effects in supraventricular and ventricular extrasystoles in 23 patients with extrasystoles of different origin [272].

Ischemia related arrhythmias were also effectively reduced by tiapamil as in patients with coronary disease and AF it decreased the VR by 54 %, although SR was not restored. The median frequency of VPC decreased just as the median ectopic/sinus beat ratio. Hypotension and bradycardia were observed in 5 out of 20 patients [273]. Similar results were reported in another article but tiapamil was effective both against supraventricular premature complexes and VPCs in contrast to other CCAs [274]. In AMI patients, tiapamil effectively reduced the number of premature ventricular contractions [275], supraventricular extra beats [276] and HR to less than 90 beats/min, which latter effect was also seen in reoccurring tachyarrhythmias during successive tiapamil administrations [277]. 1 mg/kg intravenous tiapamil significantly reduced the number of exercise-induced extrasystoles in patients 3-6 weeks after AMI [278]. Tiapamil was effectively used in 32 surgical patients in the treatment of intra- and postoperative cardiac arrhythmias such as AF, supraventricular paroxysmal tachycardia and VEBs. Small doses of 0.3-0.5 mg/kg were only effective in patients with tachycardic AF. The effective dose was between 1 and 1.5 mg/kg in most other arrhythmias [279].

Anipamil

Animal studies with anipamil

There are several animal studies showing the antiarrhythmic action of anipamil in rats [280]-[282] and also in pigs [283]. Anipamil had a stronger antiarrhythmic than hypotensive effect compared to verapamil in rats [280]. Anipamil pretreatment proved to be protective against LAD ligation induced functional (monitored by ECG signs) and biochemical (creatine kinase loss) damage in rats. In reperfusion experiments (0.5 or 1 mg/kg iv. anipamil injection 30 min before 5 min ischemia) the incidence of VT and VF was markedly reduced and completely prevented by the smaller and the higher anipamil dose, respectively [281]. 2.5 mg/kg anipamil did not produce any class I or III effects tested with recording epicardial APs but depressed early plateau phase in rats [282].

On the contrary, two studies reported harmful anipamil actions. In pentobarbitone-anesthetized pigs, intravenous anipamil exerted *arrhythmogenic* action as it increased the occurrence of VT and VF. On the contrary, verapamil, in a dose which produced similar hemodynamic effects than those of anipamil, reduced the occurrence of VT and VF [135], [136]. 8-week-long anipamil treatment aggravated left ventricular dilatation and remodeling, thereby reduced survival in rats with healed infarcts and ventricular dysfunction [136].

There is no information about the anipamil plasma levels in humans but in rabbits long-term (17 weeks) application of daily doses of 1 and 10 mg/kg led to plasma levels of 0.23 and 202 ng/ml (approximately 0.44 and 388 nM), respectively [284], [285]. There are no human data about the antiarrhythmic actions of anipamil only the systolic and diastolic BP reducing [285] and anti ischemic effects of the drug were documented [286].

TABLE 4. Human studies describing the pro- and antiarrhythmic actions of phenylalkylamines.

DRUG / dose	Proarrhythmic action	Antiarrhythmic action	Reference
Verapamil / 3 x 120 mg daily for at least 5 half-lives to load	exacerbation of the arrhythmia in idiopathic VT of left bundle branch block-like morphology		[240]
Verapamil / 10 mg intravenously	increased ST-segment elevation and programmed stimulation induced ventricular fibrillation with shorter F-F intervals in Brugada syndrome		[138]

Verapamil / 10 mg intravenously over 15-30 seconds		slowed sinus tachycardia, converted PSVT to SR and reduced VR in AF and AFL patients	[216]
Verapamil / 0.075-0.15 mg/kg		conversion to SR was achieved in 48-60 % of PSVT patients	[144]
Verapamil / 10 mg intravenously		successfully converted SVTs in WPW syndrome or was without effect in WPW syndrome	[217] [233] [234]
Verapamil / 2.5-5 mg intravenously		was effective in ventricular arrhythmias refractory to other treatment in several conditions	[235] [236] [237]
Verapamil / 5 mg intravenous boluses up to 20 mg		broad complex tachycardia demonstrating RBBB was converted to SR	[239]
Verapamil / 3 x 120 mg daily for at least 5 half-lives to load		reduced VT in approximately 2/3 of the patients in idiopathic VT of left bundle branch block-like morphology	[240]
Verapamil / 5-20 mg/min intravenously		terminated paroxysmal sustained monomorphic VT, repetitive non-sustained VT or premature ventricular contractions	[241]
Verapamil / 0.2 mg/kg intravenously		reduced the number of premature ventricular complexes in catecholaminergic polymorphic VT carrying a cardiac ryanodine receptor mutation	[244]
Verapamil / 0.25-1.0 mg intracoronary		terminated all reperfusion-induced arrhythmias except for VFs and reduced various ischemia-induced arrhythmias	[246]
Verapamil / up to 20 mg in 1 mg/min increments, intravenously, titrated to effect		in supraventricular tachyarrhythmia VR was reduced below 100 beats/min in patients within 72 hours with of AMI, conversion to SR was done in most patients with AFL	[218]
Verapamil / 240 mg SR tablet daily		right ventricular outflow tract tachycardia was terminated	[247]
D600 / 100 mg per os		decreased the HR for 10 hours in AF	[259]
Tiapamil / 1 mg/kg intravenously		reduced VR and rhythm was converted to SR in some cases in AFL, AF or PSVT patients	[268]
Tiapamil / 1 mg/kg or 50 μg/kg/min for 4 h intravenously		ectopic beats were reduced in patients with atrial and ventricular premature beats, AV CT was increased in chronic AF	[269]
Tiapamil / a bolus of 2 mg/kg intravenously, 1x 1.2-1.5 g daily		restored SR and prevented tachycardias in patients with recurrent PSVT having no accessory pathway	[270]
Tiapamil / 3 x 200 mg daily per os		positive effects in supraventricular and ventricular extrasystoles	[272]
Tiapamil / 1 mg/kg then 50 μg/kg/min for 4 h intravenously		reduced ischemia related arrhythmias, decreased the VR in patients with AF	[273]
Tiapamil / 1 mg/kg then 25 μg/kg/min intravenously		reduced the number of premature ventricular contractions, supraventricular extra beats, HR to less than 90 beats/min and exercise-induced extrasystoles in patients with or after AMI	[275] [276] [277] [278]
Tiapamil / 1-1.5 mg/kg intravenously		reduced intra- and postoperative cardiac arrhythmias such as AF, supraventricular paroxysmal tachycardia and in VEBs	[279]

9.2. Benzothiazepines

Diltiazem

Animal studies with diltiazem

Antiarrhythmic actions of diltiazem on both ischemia- and reperfusion-induced arrhythmias were described in rats [287], [288]. The antiarrhythmic actions were attributed to its negative chronotropic [287] or its energy-sparing properties [288]. The protective effects of diltiazem against VF were observed in canine ischemia models [173], [174], [178] but the drug proved to be ineffective in preventing tachycardia induced atrial remodeling compared to placebo [289].

The cardiac selectivity of diltiazem was described in rabbit [28], in dog [176] and also in human preparation [27]. The EC_{50} values for vasorelaxation and negative inotropy were 277 nM and 39 μM, respectively, in rabbit tissues [28] while 0.69 and 7.2 μM in human coronary artery and right ventricular trabeculae [27]. The smallest cardiac selectivity was seen in canine tissue as blood flow rate was doubled by 21 μg while 110 μg caused a 50 % reduction in force of contraction [176].

Clinical evidence for the antiarrhythmic actions of diltiazem

Diltiazem and digoxin had additive depressant effects on SA and AV node function (increased sinus CL, AH CT, AV node functional and effective RPs) as well as on atrial function (reduced atrial RP) without significant adverse effects in patients without conduction disorders [290].

Intravenous diltiazem effectively and safely reduced HR in patients with AF or AFL. Hypotension was the most common side effect, occurring in 13 % of patients. Symptomatic hypotension was present in 3.6 % of patients, and responded to normal saline solution in all cases [291]. Similar beneficial actions were seen in another, placebo controlled study involving 113 AF or AFL patients without severe HF [292] as well as in 37 AF or AFL patients with moderate to severe congestive HF [293]. Intravenous diltiazem proved to be more effective and faster acting (in 5 min) than intravenous digoxin (acting only in 3 hours) or the combination of the two drugs in AF and AFL patients [294]. Moreover, in a study involving 180 patients with rapid AF, low-dose diltiazem (≤ 0.2 mg/kg as a starting intravenous bolus) proved to be as effective as the standard dose of 0.25 mg/kg (according to the 2006 guidelines developed by the American College of Cardiology/American Heart Association/European Society of Cardiology for the management of patients with AF) in adequate rate control but the complication of hypotension was seen significantly less frequently 18 vs. 35 % in low and standard doses, respectively [295].

Oral diltiazem treatment also effectively lowered VR in patients with AF [296] and also reduced the maximal and submaximal HRs during exercise without affecting oxygen uptake, minute ventilation, respiratory exchange ratio or BP [297]. The effects of diltiazem on exercise tolerance are controversial in chronic AF as one study found a modest improvement similarly to that observed with verapamil [229] while another found no benefit in terms of improving either exercise tolerance or CO with either diltiazem or verapamil [228]. When compared to other drugs in controlling the VR at rest and during exercise in patients with chronic AF, diltiazem (240 mg daily) proved to be least effective compared to atenolol treatment but it more effectively reduced HR during exercise compared to digoxin [298]. In chronic AF patients 240 mg/day diltiazem combined with digoxin is an effective and safe regimen and enhances digoxin-mediated control of HR both at rest and during exercise [299], [300]. The same combined treatment alleviated the symptoms in 69 % of the patients without changing the digoxin serum level [300] and was superior for control of 24-hour mean HR as compared to each drug used separately [301]. Slow-release formulation of diltiazem (120 mg twice a day) similarly to D600 (100 mg twice a day) and verapamil (120 mg twice a day) reduced peak HRs recorded during a 6-min walking test to similar extent in 18 permanent AF patients without organic heart disease but receiving oral digoxin [262].

Intravenous diltiazem effectively converted VT to SR (in 87 % of SVT patients) or slowed HR to 100 beats/min or even below (in 82 % of patients) [302]. Similar results were found in patients with inducible sustained SVT but diltiazem had no effect on the electrophysiological properties of accessory AV connections and was safe and very effective for acute tachycardia termination when the AV node was part of the reentrant circuit [303]. In another study involving 87 patients (25 with AV nodal reentry tachycardia, 60 with AV reentry associated with an accessory AV connection, and 2 with AT) the time to conversion was 3 minutes in diltiazem responding patients and the most frequent adverse response to diltiazem was hypotension in 11 % of patients [304].

The incidence of postoperative AF in 60 patients, monitored continuously for 8 days after coronary bypass grafting with extracorporal circulation, was lower by diltiazem (10 % of patients) compared to the standard prophylactic regimen of an oral beta blocker (23.3 % of patients) [305]. CCAs, especially diltiazem were found to be beneficial after non-cardiac surgery in reducing the relative risk of myocardial ischemia and SVT [306]. Moreover, diltiazem, similarly to verapamil, effectively converted broad complex tachycardia demonstrating RBBB to SR [239].

Siratiazem (LR-A113)

Animal studies with siratiazem

Siratiazem evoked an antiarrhythmic action in a rat ischemia-reperfusion model as 2 mg/kg siratiazem reduced the incidence of VF on reperfusion. It also caused a reduction of HR and MAP [115]. The antiarrhythmic effect of siratiazem was similar to diltiazem, but less potent compared to that of verapamil in rats and guinea-pigs when studied with calcium, aconitine- and ouabain-induced arrhythmias [307].

Clentiazem (TA-3090)

Animal studies with clentiazem

Clentiazem treatment did not change transmural collateral flow measured 15 min after occlusion and the area at risk in an ischemic canine model. Infarct size was reduced by clentiazem only in those animals having a collateral flow greater than 0.02 ml/min/g, but not in those with lesser collateral flow [308].

In a hamster chronic HF model, clentiazem reduced inotropy with an EC_{50} of 734 nM, similarly to that observed in normal hearts (677 nM). The coronary circulation was enhanced by clentiazem in both normal and failing hearts, although less pronounced action was detected in the latter (EC_{50} values were 56 and 15 nM, respectively) [309].

Clinical evidence for the antiarrhythmic actions of clentiazem

In 11 patients with PSVT, clentiazem (0.1 mg/kg intravenously for 3 minutes) terminated programmed electrical stimulation-induced SVT at high right atrium in 9 out of 11 cases, while diltiazem (0.2 mg/kg) was more effective as it terminated 4 out of 4 cases [310]. In patients with stable angina, as low as 40 mg/day clentiazem reduced the HR and increased exercise duration after 4 hours of medication. After 12 hours only 80 and 120 mg/day doses had antianginal action. The most frequently reported treatment-related adverse events with clentiazem were asthenia, headache (both 7.9 %), first-degree AV block and dizziness (both 4.4 %) [311].

S-2150

Animal studies with S-2150

S-2150 (**Fig. 3.**) applied to anesthetized rats (30-60 mg/kg per os or 5 mg/kg intravenous pretreatment) reduced the myocardial infarct size just as diltiazem (5 mg/kg) and verapamil (3 mg/kg) [68]. The incidence of VT and fibrillation, induced by 4 min occlusion followed by reperfusion of the coronary artery, was reduced almost to zero by 60 mg/kg S-2150. Moreover, S-2150 also decreased cardiac mechanical function and increased CF [68]. Compared to diltiazem, S-2150 was less cardiodepressive but exerted stronger vasodilatation [68]. Similarly, in anesthetized open-chest dogs, S-2150 decreased myocardial work to a greater extent compared to diltiazem while caused a comparable hypotensive effect. S-2150 more promptly improved the local myocardial stunning caused by ischemia and reperfusion and unlike with diltiazem, this effect did not accompany the energy-sparing action in ischemic/reperfused myocardium. These results suggest that S-2150 is a favorable hypotensive agent for hypertensive patients with ischemic heart disease [312].

TABLE 5. Human studies describing the pro- and antiarrhythmic actions of benzothiazepines.

DRUG / dose	Proarrhythmic action	Antiarrhythmic action	Reference
Diltiazem / 50 mg infused over 20 min, titrated to effect		broad complex tachycardia demonstrating RBBB was converted to SR	[239]
Diltiazem / intravenously 0.25 or 0.35 mg/kg/ over 2 minutes		reduced HR in patients with AF or AFL regardless the presence of absence of congestive HF	[292] [293]
Diltiazem / once 120 mg or 3x80 mg daily per os		lowered VR in patients with AF	[296]
Diltiazem / 4x60 mg per os		reduced the maximal and submaximal HRs during exercise	[297]
Diltiazem / bolus of either 150 or 300 μg/kg over 2 minutes intravenously		converted VT to SR, reduced HR to 100 beats/min	[302]
Diltiazem / continuous infusion of for 24 h (minimum dose, 0.1		reduced the incidence of AF after coronary bypass grafting	[305]

mg/kg/h)			
Diltiazem / 0.2 mg/kg intravenously for 3 minutes		terminated programmed electrical stimulation induced SVT at high right atrium	[310]
Clentiazem (TA-3090) / 0.1 mg/kg intravenously for 3 minutes		terminated programmed electrical stimulation induced SVT at high right atrium	[310]
Clentiazem / 80 and 120 mg/day		antianginal action in patients with stable angina	[311]
Clentiazem / 80 and 120 mg/day	induced first-degree AV block as a side-effect in patients with stable angina		[311]

9.3. Other CCAs

Semotiadil (SD-3211)

Animal studies with semotiadil

The tau-on of negative dromotropic action was shorter for diltiazem and longer with verapamil compared to that of semotiadil in isolated guinea-pig hearts. During AFL semotiadil has a verapamil type of action on ventricular CL, whereas the disadvantageous prolongation of maximal ventricular CL as well as the dispersion of ventricular CL with semotiadil was only about half of those found with verapamil [172].

Comparing the vascular over cardiac selectivity of semotiadil with that of diltiazem and verapamil semotiadil was more vasoselective than the other two in guinea-pigs [6]; than diltiazem in isolated perfused rat hearts [313] and in anesthetized open-chest dogs [314].

Semotiadil produced antiarrhythmic actions in anesthetized rats as the number of total ventricular premature beats occurring during ischemia as well as the incidence of reperfusion-induced VF were reduced very effectively by the drug (EC_{50} values of 11 and 372 nM, respectively) [315]. On the contrary, semotiadil (1 mg/kg) exerted no antiarrhythmic action in a canine model [316].

Levosemotiadil (SD-3212)

Animal studies with levosemotiadil

There are much more data about the antiarrhythmic actions of levosemotiadil compared to semotiadil. In anesthetized rats, levosemotiadil reduced the number of total ventricular premature beats during the ligation period with an EC_{50} of 39 nM (4 times less potently than semotiadil) and reduced the incidence of reperfusion-induced VF with an EC_{50} of 32 nM (11 times more effectively than semotiadil) [315]. Levosemotiadil (3 mg/kg) had more potent antiarrhythmic properties compared to semotiadil (1 mg/kg) as it reduced the ratio of ectopic beats in a canine model [316]. Levosemotiadil suppressed adrenaline-induced arrhythmia in dogs and showed some antiarrhythmic effect on arrhythmias induced by either digitalis or 48 hour long coronary ligation [317]. Levosemotiadil (in 1.9 mg/kg mean dose and a plasma level of 187 ng/ml, approx. 350 nM) terminated AFL after significant increase in AFL CL in a canine model [117]. Levosemotiadil (30 mg/kg/daily per os for 7 days) prevented VF in 64 % of conscious dogs at high risk for VF. HR responses to myocardial ischemia and to graded doses of isoproterenol were blunted by levosemotiadil, which had approximately half the β-blocking activity of propranolol. The combination of I_{Na} and $I_{Ca,L}$ channel and partial β-adrenergic blockades was equally effective in preventing VF as propranolol (73 %) [318]. Due to these effects the antiarrhythmic properties of levosemotiadil in ventricular arrhythmias are more pronounced compared to semotiadil.

Fantofarone (SR 33557)

Animal studies with fantofarone

Contractile responses were more potently antagonized by fantofarone (**Fig. 4.**) compared to verapamil and diltiazem aortic strips and portal veins of the rat [319]. The negative inotropic action of fantofarone was smaller and bigger than that of verapamil and diltiazem, respectively, on rabbit left atria. Fantofarone was particularly selective for vascular smooth muscle and devoid of any potent negative inotropic actions [319].

The negative chronotropic effects were greater with fantofarone than with verapamil or diltiazem on spontaneous right atrial rate of rabbit atrium [319].

Direct antiarrhythmic action of fantofarone is not documented but, in a dose of 100 mg/kg, it decreased the calcium content in rat hearts where calcium overload was induced by vitamin D3 [95]. Fantofarone, at concentrations which cause minimal alterations to normal function, can significantly improve functional recovery following an ischemic insult in the rat heart [320]. In isovolumic perfused rat heart, 20 min pretreatment of 1 μM fantofarone significantly improved the recovery of mechanical performance, metabolic activity and cytosolic pH after 18 min of ischemia. Fantofarone treatment was even more beneficial during the reperfusion period. Higher recoveries of left ventricular pressure and rate pressure product, low end diastolic pressure, significant and complete recovery of ATP and phosphocreatine pool and a fast return of cytosolic pH to normal value were detected [321]. In anesthetized dogs 25 μg/kg intravenous fantofarone induced a decrease in myocardial oxygen consumption during periods of normal but not of elevated HR. In double dose, a decrease in myocardial oxygen consumption was maintained during pacing-induced elevated HR [108].

Human data on hemodynamic effects of fantofarone

In 6 healthy volunteers a single oral administration of 100 and 300 mg fantofarone resulted in peak plasma concentrations of its active metabolite SR 33671 of 16 and 63 ng/ml, respectively [322].

Fantofarone was examined on human volunteers where 100 and 300 mg per os did not change systemic hemodynamics, although arterial pressure and CO tended to decrease slightly after 300 mg [323]. In contrast, at the regional level, fantofarone produced strong vasodilatation of arterioles and, as a consequence, significantly increased brachial and carotid blood flow. The blood flow was preferentially increased in the brachial arterioles resulting in a redistribution of CO towards the musculocutaneous tissues. Fantofarone caused a marked and long-lasting decrease in HR, but it did not affect the auriculo-ventricular CT [323]. These effects were largely mediated by its active metabolite SR 33671 [322]. The effects of fantofarone (5 mg iv. in 10 min) were tested in both before and during right atrial pacing (100 beats/min) in 9 patients with coronary artery disease and normal systolic left ventricular function. Without atrial pacing, fantofarone decreased HR, MAP, left ventricular dP/dt_{max} and rate-pressure product; increased stroke volume index but had no effect on cardiac index, filling pressures or systemic vascular resistance. During the pacing phase, none of the hemodynamic parameters differed from baseline including especially dP/dt_{max}. Fantofarone has negative chronotropic action but shows no direct negative inotropic effect in patients with normal systolic left ventricular function [324]. Fantofarone, in doses of 100-150 mg twice daily, was effective and safe in the treatment of patients with chronic, stable angina pectoris as the drug prolonged exercise time without any effect on systolic BP both at rest and during exercise. Sinus bradycardia occurred in approximately 10 % of the patients [325].

SR 33805

Animal studies with SR 33805

In isolated rabbit atrial preparations, SR 33805 exerted weaker negative chronotropic and inotropic response (EC_{50} values of 6 and 12 μM, respectively) compared to fantofarone, verapamil and diltiazem. In superfused rat aortic strips and in femoral, renal and basilar arteries, SR 33805 reduced potassium-induced contractile responses (IC_{50} approximately 40 nM) to a similar extent to those seen with fantofarone, verapamil and diltiazem. Moreover, unlike other CCAs, SR 33805 also reduced serotonin-induced contractions (IC_{50} approximately 250 nM). SR 33805 is a potent CCA highly selective for vascular smooth muscle and devoid of any potent negative inotropic actions [79].

Beneficial actions of SR 33805 include the reduction of calcium overload induced with vitamin D3 and its deleterious consequences (lesions appearing in the tissue adjacent to the arteries) of rat hearts (per os 30 mg/kg) [95], the restoration of myocardial infarction-altered cell shortening without affecting the calcium transient amplitude in cardiomyocytes isolated from rat with end-stage HF and the improvement of end-systolic strain and fractional shortening of hearts with myocardial infarction in vivo (a single intra-peritoneal bolus of 20 mg/kg) [189].

SR 33805 was more effective in reducing calcium overload compared to fantofarone and verapamil [95].

BRL-32872

Animal studies with BRL-32872

Proarrhythmic actions of BRL-32872 were rare as in guinea-pig papillary muscle 1 μM produced EADs in only one experiment (out of 35) which was suppressed at 3 μM [41] and in canine Purkinje fibers EADs were never detected [190].

BRL-32872 can be very useful in antiarrhythmic treatment due to the lack of reverse frequency-dependent effect on APD and the relative absence of EADs. The ability of BRL-32872 to antagonize EADs produced by E-4031 in guinea-pig papillary muscle [41] or by clofilium in canine Purkinje fibers [190] adds to its antiarrhythmic potential. Moreover, BRL-32872 limited the increase in APD heterogeneity between ventricular muscle and Purkinje

preparations which might also represent the basis for its antiarrhythmic action [190]. 0.1-1 μM BRL-32872, similarly to flecainide and dofetilide, significantly lengthened CL of AF, prolonged ERPs and reduced AF inducibility in a model of acute stretch-related AF in isolated rabbit hearts, [326][327].
In vivo experiments also support the antiarrhythmic actions of BRL-32872. The incidence of VF was reduced to 13 and 0 % by 0.3 and 1.0 mg/kg intravenously given BRL-32872, respectively, compared to 66 % observed without the drug in minipigs with 20-min LAD occlusion. The antifibrillatory effects of BRL-32872 and dofetilide were associated with a prolongation of QT interval on ECG. The protective effect of BRL-32872 was greater compared to dofetilide during early reperfusion and this was most likely due to its calcium channel blocking activity [327]. This was confirmed as BRL-32872 was more potent than E-4031 in reducing the severity of arrhythmias whereas verapamil was without effect in a canine model. Combination of E-4031 with verapamil provided a similar degree of protection to that observed with BRL-32872 [328]. Similarly, in anesthetized rabbits sensitized to develop TdP, BRL-32872 (10 μg/kg/min) prolonged QT interval without inducing TdP. Classical class III antiarrhythmic agents including E-4031 and dofetilide increased QT interval and induced TdP in 50-90 % of the rabbits. The addition of verapamil reduced the incidence of TdP induced by E-4031 [328].

KT-362

Animal studies with KT-362

Antiarrhythmic actions of KT-362 were detected in anesthetized dogs subjected to a 15-min or 90-min LAD occlusion followed by 3 hours of reperfusion. KT-362 treatment (0.3 mg/kg/min intravenously started 10-15 min before and continued throughout the occlusion) reduced the incidence of reperfusion-induced VF and markedly improved myocardial segment shortening of the ischemic-reperfused region. Moreover, myocardial infarct size was reduced by KT-362 [329][330].
KT-362 (10 mg/kg intravenously) suppressed coronary ligation arrhythmia and induced a transient hypotension in a canine model. Oral administration of 70-100 mg/kg was also effective on 24 hr coronary ligation arrhythmia but it produced no prominent hypotension. KT-362 was more effective against digitalis- and adrenaline-induced arrhythmias as the required doses were only 3 and 1 mg/kg, respectively [331].
There are several studies where a comparison of KT-362 with other CCAs is made. Verapamil, but not KT-362, significantly increased CF in guinea-pig hearts. EC_{50} values for negative inotropy, chronotropy and dromotropy were about 25, 3 and 3 times lower for verapamil compared to those with KT-362 [42]. Verapamil was again more potent than KT-362 in anesthetized dogs as prolongation of PQ interval on the electrocardiogram was observed with 0.1 mg/kg verapamil but KT-362 even at 10 mg/kg evoked no negative dromotropic action [332][333]. In anesthetized ischemic dogs KT-362 (0.3 mg/kg/min intravenously started 10-15 min before and continued throughout the occlusion) but not diltiazem (15 and 30 μg/kg/min) produced a significant decrease in HR and dP/dt_{max} [333]. In rabbit aorta in the absence of extracellular calcium, responses to norepinephrine and methoxamine were inhibited by KT-362 (1-100 μM) but not by verapamil or diltiazem (10 μM each) [191].

Mibefradil (RO 40-5967)

Animal studies with mibefradil

Mibefradil evoked antiarrhythmic action in Langendorff-perfused rat hearts. VF occurring during 30 min regional ischemia was abolished by 600 nM mibefradil but reperfusion-induced VF incidence was not changed [334]. Similar results were found in open chest pigs where the low (clinically relevant) dose of mibefradil prevented the fall of the VF threshold, without depressing contractility during the ischemic period. The double mibefradil dose was antiarrhythmic during ischemia and during reperfusion, at the cost of depressed contractile activity [335], [336]. In dogs with healed infarctions, mibefradil (125-1000 μg/kg) prevented programmed electrical stimulation evoked arrhythmias during ischemia [174]. Rapid atrial pacing (400 bpm) for 7 days decreased atrial ERP and increased ERP heterogeneity, AF duration, and AF inducibility by single extrastimuli in dogs. Mibefradil treatment (100 mg/day throughout the 7 days of pacing but not that of acute administration) strongly attenuated tachypacing induced changes in ERP, AF duration and inducibility [289][336].
The cardiac selectivity of mibefradil was described in many species. EC_{50} of negative inotropy was 12 times higher than the one which doubled CF in guinea-pig whole hearts [49]. Mibefradil increased CF with an EC_{50} of 54 nM and reduced contractility of myocardium and aorta with EC_{50} values of 14 μM and 275 nM, respectively [337]. In human small arteries, the potassium contractures and isoprenaline-stimulated right atrial contractions were inhibited with IC_{50} values of 603 nM and 24.5 μM, respectively, indicating a high (41) vascular selectivity of mibefradil [8]. 300 and 600 nM mibefradil showed a marked vascular selectivity in Langendorff-perfused rat hearts [334]. In open chest pigs, the low (clinically relevant) dose of mibefradil increased left ventricular blood flow without depressing contractility [335][336].

Comparing the extent of the effects of mibefradil with other CCAs in guinea-pig ventricular cells, the negative inotropic action of mibefradil was more potent than that of diltiazem (EC_{50} values of 6.3 and 31.6 μM, respectively) [338]. On the contrary, in conscious normotensive rats, intravenous mibefradil possessed the smallest negative inotropic action compared to both verapamil and diltiazem [339]. In isovolumically beating perfused control and early phase HF rabbit hearts, mibefradil did not exert negative inotropic action up to 10 μM whereas both verapamil and diltiazem had a more potent effect in reducing contractility. Moreover, the negative inotropic actions of verapamil and diltiazem, but not that of mibefradil, were larger in HF than in control hearts [340]. In dogs with chronic HF intravenous mibefradil, but not diltiazem, caused significant improvement in contractility [341]. Verapamil was more potent in reducing the diastolic relaxation and developed pressure in Langendorff-perfused rat hearts [334].

Clinical evidence for the antiarrhythmic actions of mibefradil

In mild to moderate hypertension patients, after 4 weeks of per os mibefradil treatment the BP reduction as well as the prolongation of PQ interval was proportional with the measured plasma levels and only the highest dose (150 mg daily) was associated with cardiac complications related to AV block and bradycardia [193]. Acute effects of intravenous mibefradil (15 mg in 15 min followed by 25 mg in 60 min or 35 mg in 15 min followed by 45 mg in 60 min) tested on 71 patients included a reduction in sinus node recovery time, an increase of AH interval in the higher dose, and an increase of AV nodal refractoriness with both doses [342]. Sinus node automaticity was suppressed and HR was lowered comparatively more than its negative dromotropic effect on the AV node by a single dose of 100 mg mibefradil after 90 minutes [343]. In patients with higher than 40 % EF, the plasma level of 800 ng/ml achieved by intravenous administration, which is equivalent with an oral dose of 100 mg mibefradil, reduced MAP, total peripheral resistance and left ventricular end diastolic pressure; had no effect on HR but increased EF (from 52 to 58 %). In patients with low EF (less than 40 %) the same dose of mibefradil reduced HR but exerted a negative inotropic action. On the contrary, the 50 % reduced dose not only reduced HR but also improved EF. It seems therefore, that high plasma concentrations of mibefradil might produce myocardial depression in patients with HF [344]. In 309 patients with coronary artery disease, stable angina pectoris and positive exercise tests, mibefradil (in 100 and 150 mg/day doses) proved to be more effective as an anti ischemic drug compared to both amlodipine (10 mg/day) and placebo [345]. The Mach-1 study, done on 2590 congestive HF patients with a follow up of up to 3 years, showed that adjunct mibefradil treatment (50-mg/day for 1 month followed by 100 mg/day for up to 3 years) did not have a beneficial effect on total mortality and cardiovascular morbidity/mortality. Moreover, mibefradil increased risk of mortality by 14 % in the first 3 months which was not significant. Patients co-medicated with mibefradil and antiarrhythmics (class I or III), including amiodarone, had a significantly increased risk of death [346]. Mibefradil caused TdP [347] and sinus arrest [348] and interfered with the metabolism of many drugs as it is degraded by the cytochrome P450 pathway [349]. Due to the disappointing results of the Mach-1 study and the abovementioned severe side effects mibefradil was withdrawn from the market [350]. This happened only after the limited selectivity of the drug on T-type calcium channels has been discovered.

Monatepil (AJ-2615)

Animal studies with monatepil

Monatepil (**Fig. 5.**) was shown to possess α_1-adrenoceptor blocking activity [351], which could contribute to its hypotensive effect by 20-35 % [352].

Monatepil exerted antiarrhythmic action in rats as ventricular arrhythmias induced by adrenaline, as well as AT induced by aconitine was suppressed by intravenously applied monatepil (0.1-3.0 mg/kg) [353]. The antianginal effect of 0.1 mg/kg intravenous monatepil was more potent than that of diltiazem (0.3 mg/kg) in anesthetized rats [353].

Similarly, monatepil was more effective in inhibiting the potassium-induced contractile response and calcium influx in rat aorta (3 and 10 times more potent than verapamil and diltiazem, respectively) [351]. The antianginal effect of 0.1 mg/kg intravenous monatepil was more potent than that of diltiazem (0.3 mg/kg) in anesthetized rats [353]. The effects of monatepil on cardiac function and myocardial oxygen supply and demand were comparable with those of diltiazem, but the negative chronotropic and negative dromotropic effects of monatepil were less potent, therefore monatepil is a safer drug in the treatment of hypertension than diltiazem [354]. Indeed, in various hypertensive models of dogs and rats monatepil evoked an antihypertensive effect which developed more slowly and lasted longer compared to diltiazem [355]. Moreover, monatepil exerted comparable or more potent antiarrhythmic action than diltiazem or verapamil in rats but its proarrhythmic activity was less potent than that of the other two [353].

In a human study monatepil reduced both systolic and diastolic pressure without affecting the HR. In this regard it was similar to nitrendipine but monatepil had additional favorable effects on carbohydrate and lipid metabolism [356].

Human data on hemodynamic effects of monatepil

In patients with essential hypertension monatepil decreased BP to similar extent when applied alone or combined with ACE inhibitors. When monatepil was combined with β-blockers, the rate of responders and the reduction in both systolic and diastolic BP was lower compared to the other two groups [357].

Bepridil (CERM-1978)

Animal studies with bepridil

The antiarrhythmic actions of bepridil were described in ouabain-intoxicated canine Purkinje fibers [358], in rats [359], in anesthetized guinea-pigs [360] and also in isolated rabbit hearts [361].

Intravenous bepridil increased right atrial ERP and prevented VT in 33 and 50 % of chronically infarcted dogs in 5 and 10 mg/kg, respectively [362]. 5 mg/kg bepridil reduced myocardial oxygen consumption, HR, the number of VEBs and also abolished VF [109]. Similarly, in anesthetized rats, the number of total ventricular premature beats during coronary ligation and the incidence of reperfusion-induced VF were reduced with EC_{50} values of 229 and 676 nM, respectively [315]. Bepridil suppressed the aconitine-induced dysrhythmias in anesthetized cats (in 5 mg/kg given intravenously) [363] but not in mice (in 20-100 mg/kg given intraperitoneally) [359]. Bepridil proved to be beneficial in AF in dogs as 4 mg/kg intravenous bepridil increased sinus CL, prevented the development of AF and reduced the shortening of monophasic APD_{90} probably due to the inhibition of I_{KAch} [120]. Another study showed that bepridil (10 mg/kg/day) reversed the electrophysiological consequences of atrial remodeling (shortening of atrial ERP) to some extent. L-type calcium channel downregulation (at least on mRNA level) and ERP was also reversed and the latter positively correlated with α_{1C} mRNA expression [364]. Moreover, 1.8 mg/kg bepridil was protective against programmed electrical stimulation-induced VT. A correlation was found between the effective antiarrhythmic dose of bepridil and percentage changes in both the ERP for the first extrastimulus and QT_c, suggesting that a parallel and homogeneous prolongation in repolarization and refractoriness is essential for the antiarrhythmic effect of bepridil [99]. In 15 dogs, 4-8 days after myocardial infarction, 5 mg/kg intravenous bepridil prevented or significantly slowed sustained VT in 11/12 experiments. Bepridil prolonged the ERP of infarcted myocardium to a greater extent (15 %) compared to normal tissue (9 %) [365].

On the contrary, bepridil in the same dose (5 mg/kg) administered to dogs during coronary occlusion proved to be *arrhythmogenic* but it must be noted that bepridil administration during the reperfusion period absolutely prevented VF [133]. In canine Purkinje fibers, 1-10 μM bepridil evoked EAD at long CL but the triggered activity was rare [131]. Finally in a canine model no antiarrhythmic action of bepridil (1-6 mg/kg) was found [316].

Comparing the extent of the effects of bepridil to other CCAs it seems that bepridil is not the most potent CCA. Bepridil exerted less potent negative dromotropic action compared to verapamil [116] and also to diltiazem [177]. The negative inotropic action compared to both verapamil and diltiazem [175][366] was also weaker just as its negative chronotropic action compared to the two drugs [175], as well as its antiarrhythmic action compared to both semotiadil and levosemotiadil [315]. Similarly, the action of bepridil was at least 10 times less potent on HR and the AV nodal conduction compared to verapamil in Langendorff-perfused rabbit hearts [367]. The increase of CF by bepridil was smaller than that seen with diltiazem but comparable to that of verapamil [366].

In rabbit aorta SMCs only bepridil reduced both the potassium- and norepinephrine-induced contractions whereas diltiazem and verapamil inhibited only the depolarization-induced ones, and bepridil was one of the most vascular selective CCAs [366]. Unlike verapamil and diltiazem, which had no effect on ventricular level, bepridil caused a small increase in QRS and a bigger increase in RP and QT_c [177].

Clinical evidence for the antiarrhythmic actions of bepridil

Many human studies described the antiarrhythmic properties of bepridil. In 20 patients bepridil appeared beneficial in suppressing AFL, atrial and ventricular extrasystoles [368].

Regarding ventricular arrhythmias bepridil was effective in non-responding VT in the dose of a single 800 mg followed by 500-600 mg as it prevented VT initiation in 66 % of the cases and caused side effects (paralytic ileus) in only 1 patient. Three patients remained symptom-free over a follow-up of 4 to 13 months [369]. Bepridil prevented VT induction in 47 % of patients with symptomatic VT [370]. AV reentrant tachycardia was terminated in 30 % of the 20 patients by 2 mg/kg intravenous bepridil [232]. In the presence of 3 mg/kg bepridil, VT was still inducible in 19 patients out of 21 versus 20 out of 21 in the absence of bepridil indicating its limited potency to suppress VT [371]. On the contrary, intravenous bepridil (2 mg/kg) prevented the induction of sustained VT in 21 % of 38

patients. 900 mg/day bepridil was more effective as it prevented the induction of sustained VT in 50 % of patients. The response to intravenous bepridil did not predict the response to oral bepridil. The response to any form of bepridil treatment was not related to the plasma level of bepridil but was rather related to a higher left ventricular EF. In conclusion, that study suggested that oral bepridil at the dose of 600 mg/day may be useful in patients with recurrent VT [372]. During a mean follow-up of 52±44 months, bepridil (mean dose of 156 mg/day) completely suppressed ventricular tachyarrhythmias in 38 % of the patients and decreased the frequency of ventricular tachyarrhythmia recurrences by more than 75 % in 30 % of the patients [373]. In a study on 8 men with idiopathic VF, bepridil (200 mg/day) effectively reduced the frequency of VF episodes in association with prolongation of QT intervals at slower HRs [374]. In 21 patients with frequent VPCs, 900 mg bepridil for 2 days as loading followed by 12 days of 400 mg daily, reduced VPC frequency more than 70 % in 48 % of the patients. In 50 % of the patients at least a 95 % reduction in frequency of non-sustained VT was observed. Gastrointestinal and central nervous system side effects were considered to be mild and occurred in 62 % of the patients. Bepridil had moderate antiarrhythmic efficacy in patients with ventricular arrhythmias [375].

AF was usually more sensitive to bepridil and a correlation was found between the efficacy of bepridil in AF and its plasma concentration measured just before the intake of the next oral dose. The target value to obtain clinical benefit was approximately 300 ng/ml [376]. 100-200 mg/day bepridil successfully converted AF to SR in 58 % of the patients within 6 month (2.1 in average) and maintained that for 18 months in 81 % of these patients [377]. Similarly, 53 % of the 60 patients with long-lasting persistent AF were converted to SR by bepridil (100-200 mg/day for 8 weeks). Comparing these responders and non-responders revealed that the only difference was that the prolongation of fibrillation CL became significantly larger in responders suggesting that repetitive evaluation of fibrillation CL can be a feasible index to predict the efficacy of bepridil therapy [378]. Another study showed the same results (conversion in 50 % of the patients by 200 mg/day bepridil) and reached the same conclusion regarding responders [379]. When bepridil was compared to other antiarrhythmic drugs, some studies found bepridil to be superior for instance over amiodarone in patients with persistent AF as the conversion to SR was achieved in 35 % of patients with amiodarone (400 mg/day for 7 days followed by 200 mg/day) and in 85 % of bepridil receiving patients (150 mg/day for 2 weeks followed by 100 or 200 mg/day according to the age, gender, body weight, renal function and QT interval of the patients). The time elapsed till conversion was significantly shorter with bepridil (2.3 months) compared to amiodarone (3.2 months). Moreover, bepridil was also more effective in maintaining SR after conversion (50 % of patients in the amiodarone group and 75 % of bepridil patients) [380]. Similarly, in patients with AF longer than 3 months, bepridil (200-600 mg/day for 3 weeks) seemed to be more effective in conversion of the AF to SR compared to amiodarone but unfortunately also more arrhythmogenic (VT, prolongation of QT_c interval and TdP) than amiodarone with which no ventricular arrhythmias were seen [134]. Comparing bepridil to class IC drugs, their effectivity was similar (71 %) in the prevention of paroxysmal AF [381]. Bepridil (200 mg/day) proved to be more effective in reverting AF to SR alone or in combination with aprindine than electrical cardioversion [382]. Combination of bepridil with other antiarrhythmic drugs was studied as well. For instance, when 50-200 mg/day bepridil was added to a class I antiarrhythmic drug the frequency of symptomatic AF episodes was reduced to less than 10 % in 78 % of the patients and SR was restored within 3 months and maintained during the follow-up in 74 % of patients with persistent AF. During a mean follow-up period of 27±22 months, no potential complications occurred in any of the patients [383]. Again, combined therapy of bepridil (200 mg/day) and a class IC antiarrhythmic drug was more efficient for pharmacological cardioversion of refractory long-lasting persistent AF than bepridil alone [384]. Adding β-blocker (metoprolol or bisoprolol) to bepridil medication decreased the QT_c interval (to a level which was still longer compared to that with bepridil alone) and significantly decreased both the QT_c dispersion and TDR induced by bepridil [385].

As seen before, bepridil is more effective in atrial than in ventricular arrhythmias but sometimes arrhythmogenic effects were also reported as severe adverse effects. In a large trial involving 459 patients with AF or AFL, 4 % of the patients receiving 100-200 mg bepridil daily had adverse effects during an average follow-up of 20 months. Marked QT prolongation occurred in 13, bradycardia in 6 and dizziness and general fatigue in 1 patient each. TdP occurred in 4 of 13 patients usually triggered by hypokalemia and sudden decrease in HR. Therefore careful observation of serum potassium concentration and the ECG should always be done during bepridil administration, particularly in elderly patients [386]. A trial involving 90 patients demonstrated that bepridil dose-dependently reduced AF and converted it to SR. Unfortunately the AF reoccurrence was high (75 and 91 % with 200 and 100 mg/day dose, respectively) and adverse effects (VT, QT prolongation, sinus bradycardia) were frequent (approximately 10 %) indicating that the balance between benefits and risks of the drug should be individualized [387]. In 284 paroxysmal or persistent AF patients, the clinical outcome did not improve with bepridil during a median follow-up of 17 month and the probability of progression to permanent AF was 23.5 % at 5 years. QT_c

interval prolongation was observed when plasma concentrations of bepridil were higher than 800 ng/ml and TdP occurred in two patients without structural heart disease taking 200 mg daily [388].

AH-1058

Animal studies with AH-1058

AH-1058 exerted antiarrhythmic action in several species. For instance in the ouabain-induced arrhythmia model of the guinea-pig, pretreatment with AH-1058 (0.1-0.3 mg/kg, intravenously) delayed the appearance of VPC and VF in contrast to verapamil (1 mg/kg, intravenously) which failed to affect these arrhythmias [38]. In rat hearts subjected to 5-min coronary occlusion followed by 10-min reperfusion, AH-1058 (both at 0.1-0.3 mg/kg, intravenously and 2-4 mg/kg per os) inhibited the incidence of both VT and VF. In contrast, even in a higher dose (1 mg/kg, intravenously) the aconitine-induced arrhythmias were not affected in rats [38]. AH-1058 (100 µg/kg, intravenously) effectively suppressed epinephrine-, digitalis- as well as two-stage coronary ligation-induced ventricular arrhythmias in dogs and exerted weak hypotensive effects. In contrast, verapamil suppressed only the epinephrine-induced ventricular arrhythmia and produced severe hypotension. These results indicate that AH-1058 may possess a more selective inhibitory action on calcium channels in the heart than on those located in the vessels. The antiarrhythmic actions of either intravenously or orally administered AH-1058 did not correlate with drug plasma concentrations and were slower in onset and longer lasting than those of verapamil [389].

AP-792

Animal studies with AP-792

AP-792 (**Fig. 5.**) proved to possess antiarrhythmic properties using the epinephrine-, digitalis- and two-stage coronary ligation-induced canine ventricular arrhythmia models as intravenous administration of AP-792 (0.3 or 1.0 mg/kg) effectively suppressed each of the ventricular arrhythmias and its antiarrhythmic action was slow in onset and long-lasting [390].

TABLE 6. Human studies describing the pro- and antiarrhythmic actions of other CCAs.

DRUG / dose	Proarrhythmic action	Antiarrhythmic action	Reference
Mibefradil (RO 40-5967) / 150 mg daily per os	induced cardiac complications related to AV block and bradycardia		[193]
Mibefradil / applied as co-medication	caused TdP		[347]
Bepridil / 200-600 mg/day for 3 weeks	in persistent AF patients VT, prolongation of QTc interval and TdP was observed		[134]
Bepridil / 200-600 mg/day for 3 weeks	in patients with persistent AF, induced VT, prolongation of QTc interval and TdP more often compared to amiodarone		[134]
Bepridil / 100-200 mg/day	induced QT prolongation, bradycardia, TdP usually triggered by hypokalemia, sudden decrease in HR in patients with AF or AFL		[386]
Bepridil / plasma level of approximately 300 ng/ml		suppressed AF	[376]
Bepridil / 100-200 mg/day		successfully converted AF to SR in about half of the patients	[377] [378]
Bepridil / 150 mg/day for 2 weeks followed by 100 or 200 mg/day		converted AF to SR in shorter time and maintained SR for a longer period compared to amiodarone	[380]
Bepridil / applied as co-medication with various antiarrhythmic drugs		prevented paroxysmal AF, converted AF to SR in persistent AF	[381] [382] [383]
Bepridil / a single dose of 800 mg followed by 500-600 mg		prevented VT initiation in non-responding VT patients	[369]
Bepridil / 2 mg/kg intravenously		terminated AV reentrant tachycardia in a third of patients	[232]
Bepridil / 900 mg/day		prevented the induction of sustained VT in 50 % of patients	[372]
Bepridil / mean dose of 156 mg/day		suppressed ventricular tachyarrhythmias and decreased the frequency of ventricular tachyarrhythmia recurrences in 30 % of the patients	[373]
Bepridil / 200 mg/day		reduced the frequency of VF episodes in idiopathic VF	[374]
Bepridil / 900 mg for 2 days followed by 400 mg/day		moderate antiarrhythmic efficacy in patients with ventricular arrhythmias	[375]

10. Concluding remarks

As was shown in this review, class IV agents, acting through several mechanisms, provide antiarrhythmic action against mainly supraventricular tachyarrhythmias. These drugs, especially the compounds of phenylalkylamine group, are unfortunately not entirely devoid of proarrhythmic side effects. These side effects could

probably be minimized with inhibition of other ion channels making these compounds to be able to target multiple sites. This clearly could be observed with BRL-32872 or AH-1058. Other compounds like monatepil (AJ-2615) can have a potentially useful side effect (lowering blood pressure) due to the blockade of alpha-1 adrenergic receptors.
Nowadays the discovery of new pharmacological targets to treat cardiac arrhythmias is a rapidly growing area of research. Relatively new targets include for instance gap junction proteins or ion channels like I_{KAch}, I_{Kur}, which chennels can not be found on the entire myocardium. But the successful application of amiodarone and bepridil in the antiarrhythmic therapy reminds us that a compound with multiple target sites is probably as good as, if not better, than a very selective ion channel blocker.
Another conclusion based on this review can be that mother compounds like verapamil and diltiazem in the group of phenylalkylamines and benzothiazepines, respectively, are still very much used in the medical practice. This is the case regardless the existence of numerous newer derivatives. These newer compounds can actually be more selective to inhibit the L-type calcium channels but their other effects make them less likely to have an advantage over the mother compound. This highlights the long and cumbersome process of drug design.
CCAs are still in use for antiarrhythmic therapy but their indication is very narrow. These drugs are not the first choice to be given in most cases but both verapamil and diltiazem are recommended for both acute and long-term rate control of AF as well as in AF associated with hyperthyroidism when beta-blocker is contraindicated. The application of these non-dihydropyridine compounds should also be considered in AF with pulmonary disease and acute coronary syndrome.

LIST OF ABBREVIATIONS

AF: atrial fibrillation
AFL: atrial flutter
AMI: acute myocardial infarction
AP: action potential
APA: action potential amplitude
APD: action potential duration
ATP: adenosine triphosphate
AV: atrioventricular
BK_{Ca}: large-conductance calcium-activated potassium channel
BP: blood pressure
CCA: calcium channel antagonist
CF: coronary flow
CL: cycle length
CO: cardiac output
CT: conduction time
dP/dt_{max}: maximal rate of pressure rise
EAD: early afterdepolarization
EC_{50}: half-effective concentration
ERP: effective refractory period
HEK: human embryonic kidney
hERG: human ether-a-go-go
HF: heart failure
HR: heart rate
IC_{50}: half-inhibitory concentration
$I_{Ca,L}$: L-type calcium current
$I_{Ca,T}$: T-type calcium current
I_{K1}: inward rectifier potassium current
$I_{K,Ach}$: acetylcholine-activated potassium current
$I_{K,ATP}$: ATP dependent potassium current
$I_{K,Na}$: sodium activated potassium current
I_{Kr}: rapid component of delayed rectifier potassium current
I_{Ks}: slow component of delayed rectifier potassium current
I_{Kur}: ultrarapid component of delayed rectifier potassium current
I_{Na}: sodium current
I_{NCX}: Na^+/Ca^{2+} exchange current

I_{to}: transient outward potassium current
LAD: left anterior descending coronary artery
LQTS: long QT syndrome
MAP: mean arterial pressure
MDP: maximal diastolic potential
PSVT: paroxysmal supraventricular tachycardia
RBBB: right bundle branch block
RMP: resting membrane potential
RP: refractory period
SA: sinoatrial
SMC: smooth muscle cell
SR: sinus rhythm
SVT: supraventricular tachycardia
TdP: torsade de pointes
TDR: transmural dispersion of repolarization
VEB: ventricular ectopic beat
VF: ventricular fibrillation
V_{max}: maximal rate of depolarization
VPC: ventricular premature complex
VR: ventricular rate
VT: ventricular tachycardia
WPW: Wolff-Parkinson-White

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