Table S1. Summary of main experimental studies of ranolazine.

Anti-Angina/Ischemia			
Mode of action	*Mechanism*	*Targets*	*Ref*
Improvement of metabolism	- Shift of energy production from free fatty acid to glucose oxidation by inhibiting fatty acid. Increase in efficiency of ATP production	Inhibition of 3-ketoacyl coenzyme A thiolase / activation of the pyruvate deshydrogénase	[1–12]
Improvement of diastolic function	-Ionic homeostasis (Sodium, Calcium)	Block of $I_{Na,late}$	[13–15]
	-Improvement of relaxation	Direct modulation of myofilament Ca^{2+} sensitivity.	[16]
Atrial Anti-Arrhythmics			
Mode of action	*Mechanism*	*Targets*	*Ref*
Decrease atrial excitability	- APD lengthening, prolongation of ERP, increase in the excitation threshold during diastole and lengthening of conduction time / Decrease of EAD / DAD.	Block of $I_{Na,peak}$ and $I_{Na,late}$	[17–24]
	-Decrease in ectopic activity in pulmonary vein sleeve / Decrease of EAD / DAD	Block of I_{Na}	[25]
Ventricular Anti-Arrhythmic			
Mode of action	*Mechanism*	*Targets*	*Ref*
Decrease ventricular excitability	- APD shortening and reduction of the dispersion of ventricular repolarization and beat-to-beat variability of APD / Decrease of EAD	Block of $I_{Na,late}$	[26–34]
	-Prolongation of ERP	Block of $I_{Na,late}$	[32,35–38]
Decrease ventricular excitability	-Indirect normalization of intracellular Ca^{2+} / Decrease of DAD	Block of $I_{Na,late}$	[15,39–45]
Autonomic Modulation			
Mode of action	*Mechanism*	*Targets*	*Ref*
Normalization of cardiac autonomic control	-Possible direct effect on the autonomic nervous system	Possible involvement of Na_v blocking	[46–48]
		Undetermined	[49]
	-Normalization of alpha-1 adrenergic receptor -Adrenergic receptors antagonization	Beta-1 and Beta-2 adrenergic receptors	[50,51]
Genetic Epilepsy			
Mode of action	*Mechanism*	*Targets*	*Ref*
Decrease of abnormal neuronal firing	-Inhibition of persistent Na current	Block of $Na_v1.1$ (neuronal)	[52]
	-Inhibition of persistent Na current	Block of $I_{Na,late}$	[53]
Decrease seizure frequency in a mouse model of epilepsy	-Attenuation of abnormal AP firing in pyramidal neurons.		[54]
Neuropathic Pain			
Mode of action	*Mechanism*	*Targets*	*Ref*
Decrease of ectopic activation	Inhibition of persistent Na current	Block of $Na_v1.7$ (neuronal)	[55–58]
Beneficial Vascular Effects			
Mode of action	*Mechanism*	*Targets*	*Ref*
Improvement of tissue perfusion	Smooth muscle cells Relaxation	Na_v and anti-alpha-1 adrenergic receptor	[59–66]
Diabetes and related diseases			
Mode of action	*Mechanism*	*Targets*	*Ref*
Normalization of hemoglobin A(1c)	Increase in β-cell survival and improvement of glucose homeostasis	Undetermined	[67–71]
Pulmonary art. hypertension			
Mode of action	*Mechanism*	*Targets*	*Ref*
Improvement of oxygen supply	Improvement of pulmonary hemodynamics / Anti-remodeling effect (right ventricle)	Block of $I_{Na,late}$	[66,72,73]
(Para)Myotonia congenita			
Mode of action	*Mechanism*	*Targets*	*Ref*
Improvement of muscle stiffness	Inhibition of the sustained and excessive firing of skeletal muscle AP	Block of $I_{Na,late}$	[74–76]

Oncology			
Mode of action	*Mechanism*	*Targets*	*Ref*
Reduction of cancer progression	Decrease in invasiveness and cell metastasis	Block of Na_v channel (mainly $Na_v1.7$, $Na_v1.6$, and $Na_v1.5$), $I_{Na,late}$	[77,78]
		Limitation of Lipid metabolism	[79]
Cardioprotective effect	Improvement of diastolic function	Decreased ROS production and oxidative stress	[80–82]

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