# Verapamil: prevention and treatment of cardio-renal syndromes in diabetic hypertensive patients?

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**Abstract.** – **Patients with diabetes mellitus (DM) often present other chronic comorbidities including arterial hypertension (AH), chronic kidney disease (CKD), ischemic heart disease (IHD) and heart failure with preserved ejection fraction (HFpEF). The frequent association of the latter conditions is considered part of the spectrum of cardio-renal syndromes (CRS), a group of disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. Verapamil is a non-dihydropyridine calcium channel blocker (CCB) widely used in the treatment of hypertension, chronic stable angina, secondary prevention of reinfarction, paroxysmal supra-ventricular tachycardia and for rate control in atrial fibrillation/flutter. In addition to its antihypertensive and anti-ischemic actions verapamil exerts favorable effects also on glycemic control, proteinuric diabetic nephropathy, left ventricular diastolic dysfunction and sympathetic nervous system overactivity which may potentially benefit patients with DM and CRS. In this narrative review, we summarize the current evidence on the potential role of verapamil in the prevention and treatment of CRS in diabetic hypertensive patients.**

*Key Words:*
  *Verapamil, Cardio-renal syndromes, Hypertension, Diabetes mellitus, Proteinuria, Ischemic heart disease, Heart failure with preserved ejection fraction, Diabetic nephropathy.*

## Abbreviations

DM: Diabetes Mellitus; DN: Diabetic Nephropathy; AH: Arterial Hypertension; CKD: Chronic Kidney Disease; HF: Heart Failure; HFpEF: Heart Failure with preserved Ejection Fraction; CRS: Cardio-Renal Syndromes; ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin-II Receptor Antagonists; CCB: Calcium Channel Blocker; BP: Blood Pressure; LCC: L-type Calcium Channel; TCC: T-type Calcium Channel; EF: Ejection Fraction; IHD: Ischemic Heart Disease; RAAS: Renin-Angiotensin-Aldosterone System; ACE: Angiotensin-Converting Enzyme; AT1: Angiotensin II type 1- receptor subtype; HFrEF: Heart Failure with Reduced Ejection Fraction; WRF: Worsening of Renal Function; TXNIP: β-cell Thioredoxin-Interacting Protein; Tr/Ve: Trandolapril/Verapamil; DBP: Diastolic Blood Pressure; non-DHP: non Dihydropyridine; PDGF: Platelet-Derived Growth Factor; PAF: Platelet-Activating Factor; LV: Left Ventricular; SNS: Sympathetic Nervous System; BRS: Baroreflex Sensitivity, MSA: Muscle Sympathetic Activity; MI: Myocardial Infarction; UACR: Urinary Albumin Creatinine Ratio.

## Introduction

Patients with diabetes mellitus (DM) often present several comorbidities including arterial hypertension (AH), chronic kidney disease (CKD), ischemic heart disease (IHD) and heart failure (HF), even with preserved ejection fraction (HFpEF). The simultaneous manifestation of heart and kidney disease has led to the definition of a new clinical entity: the cardio-renal syndromes (CRS). CRS represent a group of disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other[1,2] (Figure 1).

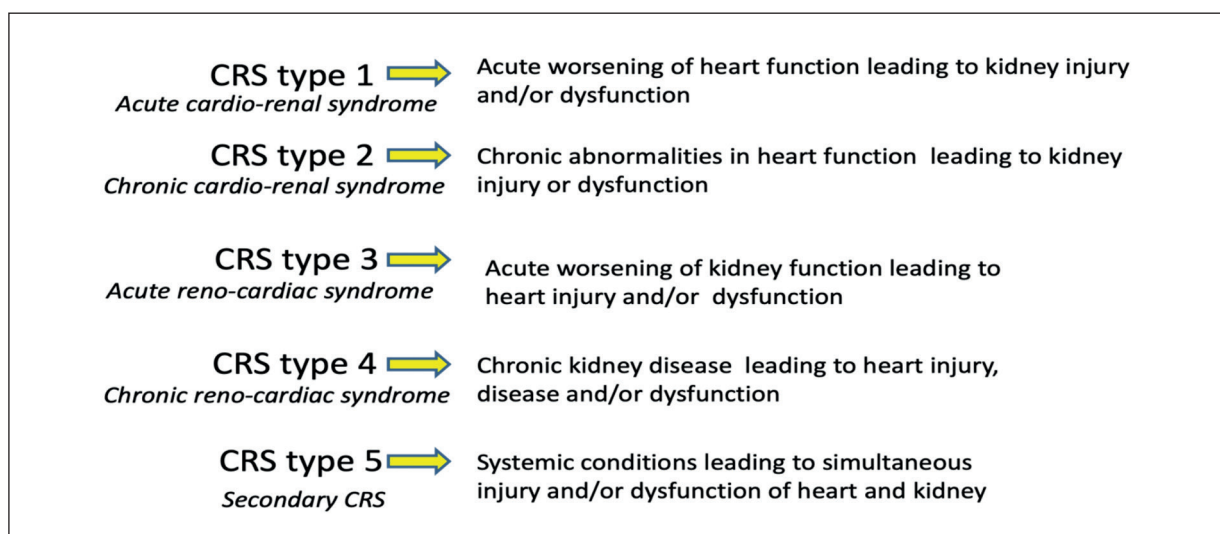*Corresponding Author:* Paolo Lido, MD; e-mail: paulshore@virgilio.it

**Figure 1.** Cardio-renal syndromes: definitions and classification.

Among CRS, DM is considered the primary determinant of type 5 CRS, that is a situation in which a systemic disease leads to simultaneous injury and/or dysfunction of the heart and kidney[1].

Currently, the treatment of CRS is empirical, based on angiotensin converting enzyme inhibitors (ACEIs), angiotensin-II receptor antagonists (ARBs), beta-blockers and diuretics. Typically, these patients have an hypervolemic state and consequently require more intensive diuretic treatment with loop diuretics[1].

Therapy of CHF with concomitant renal impairment is still not evidence-based, as these patients are generally excluded from CHF trials[1]. Guidelines suggest the use of SGLT-2 Inhibitors and GLP-1 agonists in patients with type 2 DM and CRS[2]. These new drugs are expensive, and we don't know their long-term safety profile.

Therefore, identifying other older drugs, cheaper, affordable that could be safely used in patients with DM and CRS is mandatory. Among these older drugs, non-dihydropyridine calcium channel blocker (CCB) has not yet been considered despite these drugs are widely used in the treatment of several cardiovascular diseases and their complications[3-5]. As an example, a drug like verapamil, in addition to its antihypertensive and anti-ischemic actions exerts favorable effects also on glycemic control, diabetic nephropathy, left ventricular diastolic dysfunction, and sympathetic nervous system (SNS) overactivity, all mechanisms that are involved in the pathophysiology of

CRS[1,2,6-10] and that, as such, could benefit patients with DM and CRS, particularly the type 5. In this narrative review we summarize the current evidence on the potential role of verapamil in the prevention and treatment of CRS in diabetic hypertensive patients.

### Verapamil: Mechanisms of Action and Pharmacokinetics

CCBs inhibit the flow of extracellular calcium through ion-specific channels that span the cell wall[11,12]. CCBs are divided in two chemical structure subclasses: dihydropyridines and non dihydropyridines (non-DHPs)[11,12]. Verapamil is a non-DHP CCB. When inward calcium flux is inhibited, vascular smooth muscle cells relax, resulting in vasodilation and blood pressure (BP) lowering[12]. Although several types of calcium channels have been identified, the L-type channels are those mainly blocked by CCBs in humans.

No-DHPs differ in important ways from the dihydropyridines. One of the main differences is that the two subclasses of CCBs bind to separate sites on the L-type calcium channel (LCC)[12]. Non-DHPs, likely verapamil, bind to a receptor on the α-1 component of LCC, whereas dihydropyridines bind to another sub-receptor type on the alpha-1 component of the L-type channels, resulting in markedly different pharmacologic properties[13]. Importantly, verapamil at variance with most of dihydropyridines has the property of also inhibiting the T-type calcium channel (TCC)[14].

As far as the effects are concerned, dihydropyridines tend to reflexively increase heart rate[13], whereas no-DHPs slow the sinoatrial node and atrio-ventricular conduction velocities, and as such, exert a negative chronotropic effect that results useful for acute treatment and chronic prevention of supraventricular tachyarrhythmias[12,15,16].

The hemodynamic actions of verapamil are characterized by a complex interplay of changes in preload, afterload, heart rate, and coronary blood flow. It does not depress cardiac systolic function, except in HF with severe reduction of ejection fraction (EF)[17-19]. The drug has a balanced profile of cardiac and peripheral effects. It lowers heart rate, increases myocardial perfusion, and reduces coronary spasm dilating coronary arteries[20].

Verapamil reduces total peripheral resistance lowering high blood pressure by vasodilation[21,22]. Because of its user-dependent action on the voltage-operated calcium channel, the effects of verapamil are more pronounced on high than on normal blood pressure[23-26]. As early as day one of treatment, blood pressure falls; the effect is found to persist also in long term therapy. Verapamil is suitable for the treatment of all types of hypertensions: for monotherapy in mild to moderate hypertension; combined with other antihypertensives in more severe types of hypertensions[23,27-29].

Controlled trials have established its role in Prinzmetal's variant angina, unstable angina, and chronic stable angina. It has also been found to be effective in obstructive cardiomyopathies. Moreover, verapamil has a non-competitive sympathetic antagonist effect[15,23]. The drug is eliminated by hepatic metabolism, with excretion of inactive products in the urine and/or faeces[16].

Renal disease has no impact on the pharmacokinetics of verapamil[17] in fact the drug is effective and well tolerated in patients with hypertension associated with CKD[18]. No changes in dose or mode of application of verapamil are recommended with any stage of CKD or any type of renal replacement therapy. The terminal elimination rate constant, clearance, volume of distribution, and bioavailability of verapamil are not significantly different between patients undergoing maintenance hemodialysis and normal subjects[19,22]. *In vitro* metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil is, at the same time, inhibitor of CYP3A4 enzymes and inhibitor of P-glycoprotein (P-gp) thus, patients should be monitored for drug interactions[23].

### RAAS Inhibitors: Mechanisms of Action and Precautions for Use

The renin-angiotensin-aldosterone system (RAAS) plays an integral role in the pathophysiology of AH because it affects the regulation of fluid volume, electrolyte balance and blood volume[30]. Renin, an enzyme produced primarily by the juxtaglomerular cells of the kidney, catalyzes the conversion of angiotensinogen into an inactive substance, angiotensin I[30]. Angiotensin-converting enzyme (ACE) then converts angiotensin-I to the physiologically active angiotensin II which causes potent vasoconstriction and aldosterone secretion[30]. ACE inhibitors block the conversion of angiotensin I to angiotensin II[30]. ARBs act by binding to specific membrane-bound receptors that displace angiotensin II from its type 1–receptor subtype (AT1). These drugs therefore function as selective blockers of the major downstream targets of Angiotensin II[31]. Angiotensin II pressor effects are mediated by AT1 receptors. These receptors are widespread in organs and tissues but are found predominately in vascular and myocardial tissue, the liver, the adrenal cortex (i.e., the zona glomerulosa tissue which secretes aldosterone) and some areas of the brain[31].

Clinical trials have clearly shown the efficacy of ACEI and ARBs in the treatment of patients with HF and reduced ejection fraction (HFrEF), meanwhile neutral results have been observed in patients with HFpEF[32].

It is well known that up to one-half of patients with HF have preserved ejection fraction (HFpEF)[32]. Dysregulation of the RAAS has also a critical role in the pathogenesis of CKD and diabetic nephropathy[30]. ACEIs and ARBs, reducing the intraglomerular pressure, reduce proteinuria in both diabetic and non-diabetic nephropathy with proteinuria but unfortunately may cause worsening of renal function (WRF). Moreover, administration of ACEIs or ARBs may cause hyperkaliemia overall in diabetic patients even in absence of CKD, because DM itself is a risk factor for hyperkaliemia and because of the frequent concomitant condition of hyporeninemic hypoaldosteronism in these patients[1,30,33-35].

In a real-world, retrospective study has been shown that in a cohort of HF patients under re-

nin–angiotensin–aldosterone system inhibitors, subjects with hyperkalemia had an increased risk of cardiovascular events or death compared to patients without hyperkalaemia[36]. Furthermore, in a clinical trial, the initiation of irbesartan treatment, an angiotensin receptor blocker (ARB), in patients with HFpEF has been associated with excess risk of WRF, in contrast to WRF occurring with RAAS blockade in patients with HFrEF observed in previous clinical trials[37].

### Verapamil, Inhibition of β-Cell Apoptosis and Lowering Blood Glucose Levels in Diabetic Patients

Type 1 and type 2 DM are characterized by progressive β-cell failure. Apoptosis is probably the main form of beta-cell death in both forms of the disease[38]. Glucose and DM upregulate β-cell thioredoxin-interacting protein (TXNIP) expression, and TXNIP overexpression induces β-cell apoptosis[39]. Orally administered verapamil reduced TXNIP expression and β-cell apoptosis, enhanced endogenous insulin levels, and rescued mice from STZ-induced DM. Verapamil also promoted β-cell survival and improved glucose homeostasis and insulin sensitivity in BTBR ob/ob mice (a mice with leptin-deficiency mutation which develops severe type 2 diabetes). This verapamil-mediated TXNIP repression seems to be conferred by reduction of intracellular calcium, inhibition of calcineurin signaling, nuclear exclusion and decreased binding of carbohydrate response element-binding protein to the E-box repeat in the TXNIP promoter[39].

Hence, verapamil, inhibiting proapoptotic β-cell TXNIP expression enhances β-cell survival and function and seems to improve overt DM[39]. In "REGARDS" (Reasons for Geographical and Racial Differences in Stroke), a national cohort study of community-dwelling middle-aged and older adults, verapamil use was associated with lower fasting blood glucose levels among participants with DM. Verapamil users had on average 10 mg/dL lower serum glucose compared to CCB non-users with greater differences among insulin users: 24 mg/dL lower serum glucose among users of insulin in combination with oral agents and 37 mg/dL lower among users of insulin alone[40]. In a systematic review and metanalysis without restrictions for study type, plasma glucose levels were lowered significantly by verapamil-based treatment in patients with type 2 DM (mean change -13 ± 5.29; $p = 0.049$)[41].

Recently a randomized, double-blind, placebo-controlled study has shown at the end of the study that the mean HbA1c was significantly lower (about 0.5%) in the verapamil group than in the placebo group ($p = 0.012$) in 44 patients with diagnosis of type 2 DM treated with oral antihyperglycemic drugs, including metformin and sitagliptin[42].

Furthermore, a randomized, double-blind, placebo-controlled, phase 2 trial has shown that oral verapamil added to standard insulin therapy promotes endogenous β-cell function and lowers exogenous insulin requirements and hypoglycemic episodes in recent-onset adult type 1 DM patients[43].

Overall, verapamil was well tolerated and aside from mild constipation no clinically significant adverse events were reported. Of note, no hypotension and no EKG changes were observed either demonstrating that verapamil may also be used safely in young, normotensive subjects with type 1 DM[43].

### Verapamil and Diabetic Nephropathy with Proteinuria

DM and AH are the leading causes of end-stage renal disease[11,44]. While the presence of microalbuminuria is a strong predictor of cardiovascular complications, its progression to macroalbuminuria indicates the presence of kidney disease[45]. A strong correlation has been reported between reductions in proteinuria and a slower development of glomerulosclerosis[46]. Hence, in hypertensive patients pharmacological treatment should focus not only on BP lowering but should also attempt to lower or normalize albuminuria levels. Current guidelines recommend the use of ARBs or ACEIs in the treatment of hypertension and albuminuria in diabetic patients[45-47]. However, data from clinical trials suggest that also verapamil is associated with a reduction of proteinuria in patients presenting with DN, an effect rarely reported with dihydropyridines CCBs[23,48-50]. In particular, verapamil has been proved as effective as ACE inhibitors in reducing urinary albumin excretion and in slowing the progression of type 2 diabetic nephropathy with overt proteinuria[11,23,48-50]. Since in this type of patients BP lowering to target values is difficult to obtain, adding verapamil to RAAS inhibitors could be a valid therapeutic option to concomitantly reduce albuminuria[11,49,50].

It's reasonable to extrapolate these results to patients with type 1 DM and diabetic nephropathy with proteinuria, who may benefit from the addition of verapamil when monotherapy with an ACE inhibitor or ARB fails to provide an ad-

equate response. Furthermore, verapamil should also be considered when ACE inhibitors and/or ARBs are contraindicated[11].

Consistent with these data, a meta-analysis of randomized controlled trials indicates that the association therapy trandolapril/verapamil (Tr/Ve) provides an advantage over trandolapril monotherapy by reducing diastolic blood pressure (DBP) and albuminuria to a greater extent than ACE-inhibitor alone[51].

It is also true that the "BENEDICT A" and "BENEDICT B" randomized studies failed to show a benefit of Verapamil in the prevention and the treatment of diabetic nephropathy in type 2 DM, thus, there is conflicting evidence about a possible nephroprotective effect of verapamil[52,53].

A more recent article that reviewed the literature to assess the use of non-DHP CCBs for the treatment of proteinuria in diabetic and non-diabetic kidney disease examining 13 clinical trials in which verapamil was the most common agent studied concluded that "non-DHP CCBs may be a reasonable therapeutic option for patients with diabetic kidney disease and persistent proteinuria despite maximum doses of ACE inhibitors or ARBs. Additionally, they may be reasonable alternatives to ACE inhibitors or ARBs if a contraindication or intolerance exists"[54]. The mechanisms of the possible favorable effects of verapamil at the level of the kidney are still to be defined. Several effects of CCBs might contribute to protect the kidney including attenuation of mesangial entrapment of macromolecules, antagonism of the mitogenic effect of platelet-derived growth factor (PDGF) and platelet-activating factor (PAF) and the suppression of mesangial cell proliferation[54,55]. In addition this class of drugs may also act as scavengers of free radicals, inhibits the renal effects of endothelin[45,47,50] and cytokine production thereby suppressing mesangial cell proliferation and reducing glomerulosclerosis *in vivo*[56]. Moreover, verapamil seems to reduce albuminuria by improving glomerular selective permeability and lowering renal perfusion pressure[12,50]. A large body of evidence indicates that voltage-gated calcium channel subtypes, including L-, T-, N-, and P/Q type, are present within the renal vascular and tubular tissues, and that blockade of these channels may exert several beneficial effects on the renal microcirculation[56,57]. For instance, inhibition of the TCC present on both afferent and efferent arterioles elicits vasodilation, leading to the reduction in glomerular

pressure. In addition, TCC inhibition opposes inflammatory processes in the glomerulus and interstitium and facilitates natriuresis[57,58]. It is reasonable to speculate that the nephroprotective effects of verapamil are due to its capacity to block the TCC in addition to the L-type channels[14]. Furthermore, verapamil has antioxidative properties and has been shown to reduce the degree of ischemia-reperfusion injury in kidney tissue by inhibiting the cell death[59,60].

### Verapamil, DM, AH, IHD and HFpEF

Type 2 DM is an independent risk factor for the development of coronary artery disease and left ventricular (LV) diastolic dysfunction[61,62]. Furthermore, diabetic patients often present with AH and CKD, which also promote LV hypertrophy and abnormal diastolic function[63-65]. Because of its mechanisms of action, in this population the potential benefits of verapamil may extend to the heart by improving diastolic function. In particular, the decrease in cytoplasmic $Ca^{2+}$ concentration may improve myocardial relaxation, the control of BP may lead to regression of LV hypertrophy and the lowering of heart rate reduces myocardial oxygen consumption[8,9,65,66]. In fact, it has been demonstrated that the administration of verapamil in patients affected by mild and moderate AH results in an improvement in LV hypertrophy and LV diastolic function, normalization of BP without a corresponding deterioration in LV systolic function[66].

TCC inhibition induced by verapamil produces antihypertensive, anti-ischemic effects and afterload-reducing effects in chronic HF offering the potential for a cardiovascular protective benefit[67].

Ischemia of the myocardium results in a loss of ultrastructure and function and the intracellular accumulation of $Ca^{2+}$ appears to precipitate many of these changes[66]. The intracellular accumulation of $Ca^{2+}$ in ischemic myocardium seems to be caused by a failure of the ATP-dependent mechanisms responsible for maintaining intracellular homeostasis with respect to $Ca^{2+}$. The administration of verapamil modifies the events precipitated by an ischemic episode[68] and has been shown to reduce indexes of ischemic injury in experimental models of prolonged coronary artery occlusion and to increase significantly contractile function of the post-ischemic stunned myocardium attenuating post-ischemic contractile dysfunction[69].

Consistent with these effects in the clinical study "INVEST" in hypertensive patients after myocardial infarction, verapamil-sustained release-based

treatment strategy reduced total mortality, sudden cardiac death and reinfarction rate[23,70,71].

Verapamil has been reported to improve indexes of LV filling at rest and during exercise-induced ischemia[69,71] and in patients with HFpEF, in small studies, the administration of this drug increases exercise capacity and reduces HF score[6,72,74,75]. Moreover, verapamil blunts the hypertensive response to exercise in patients with diastolic dysfunction at rest[73] and enhances LV diastolic filling in elderly subjects[7].

Of note, in a double-blind, randomized, crossover, placebo-controlled trial diltiazem, another non-DHP CCB, reduced myocardial ischemic episodes in patients with end-stage renal disease and coronary artery disease positively modifying the circadian pattern of ischemic episodes[76].

### Verapamil and SNS in DM, AH, CHF, and CKD

The SNS is an important regulator of cardiovascular homeostasis[77]. The SNS overactivity is crucial in the pathogenesis of hypertension in DM[78]. In patients with early diabetic autonomic neuropathy, vagal impairment can lead to a relative predominance of sympathetic activity in the sympatho-vagal balance. Sympathetic overactivity stimulates RAAS activity, promotes sodium reabsorption, increases heart rate, stroke volume and peripheral vascular resistance, thus inducing AH and increasing cardiovascular risk[78]. The activity of the SNS is increased as in HF patients and as in CKD patients. Feedback activation of SNS in the setting of CKD or HF contributes to the development and progression of dysfunction in the other. DM activates these pathogenic pathways, feeding into this vicious cycle and contributing to a poor prognosis[79].

Verapamil reduces sympathetic activity and, therefore, may have a beneficial effect in diabetic patients with disturbed sympatho-vagalbalance[80,81]. The drug induces a shift in sympatho-vagal balance, as measured by heart rate variability indices, toward vagal predominance in patients with mild to moderate hypertension, also improving baroreflex sensitivity (BRS)[82]. In hypertensive patients, slow-release form of verapamil exerts a trend toward decreased muscle sympathetic activity (MSA) and decreases plasma concentrations of norepinephrine[68,71,75], angiotensin-II, and endothelin-1[76,82,83]. Verapamil, administered during the subacute phase of myocardial infarction (MI), improves both global and short-period indexes of heart rate variability (HRV) and in-

duces a shift in the sympathetic-parasympathetic interaction toward vagal predominance. This effect may contribute to an explanation of the beneficial effects of verapamil that have been reported in post-MI patients[84,85]. It could be argued that the reduction of SNS overactivity, induced by verapamil is due to its capacity to block TCC. TCC inhibition has a sympatholytic effect, owing to T-channel expression in neurons, sinoatrial and atrioventricular nodes and Purkinje fibers[69].

## Discussion

In patients with DM and AH the presence of proteinuria has been shown to be an important and independent risk for an increased incidence of cardiovascular morbidity and mortality. At the same time, proteinuria is not only a marker for renal disease, but it also predicts those patients at greatest risk for the CKD progression. Hence proteinuria is a risk factor involved in CRS progression in diabetic patients[86]. In addition, the RAAS and the SNS play, in an interdependent manner, a role in modulating the functional relationship between the two organs[86,87]. CRS could be also considered as a complex pathophysiological interplay of neurohumoral pathway activation including the SNS and the RAAS axis[87,88]. ACEIs and ARBs, have been shown to significantly reduce mortality and morbidity in patients with HFrEF, meanwhile neutral results have been observed in patients with HFpEF[88,89]. Unfortunately, the administration of these drugs may cause WRF and hyperkalaemia, overall in diabetic patients with concomitant DN[1,34,35]. Furthermore, treatment with irbesartan (an ARB) is associated with excess risk of WRF in patients with HFpEF in contrast to WRF occurring with RAAS blockade in patients with HFrEF observed in previous clinical trials[37].

In a clinical study the administration of verapamil reverts acute renal functional impairment induced by ARBs[89] and in another study in a dose-dependent manner, verapamil blocks angiotensin II-induced vasoconstriction other than alpha-1 adrenergic vasoconstriction[90].

Verapamil improves prognosis in hypertensive patients after myocardial infarction[23,66,67] and at the same time reduces symptoms in patients with HFpEF[6,73,74].

Moreover, there is a strong relationship between SNS overactivity and prognosis and there is also evidence that blockade of SNS reduces

morbidity and mortality in patients with DM[79]. In diabetic subjects, vagal activity is often reduced. The reduction results in relative or absolute sympathetic activation, which could increase cardiovascular risk[80].

However, modulation of SNS is underutilized as a strategy to protect both the diabetic kidney and the heart[79].

Verapamil reduces sympathetic activity inducing a shift in the sympathetic-parasympathetic interaction toward vagal predominance[85]. TCC inhibition induced by verapamil produces antihypertensive, anti-ischaemic effects, afterload-reducing effects, sympatholytic effects in HF and exerts at the same time nephroprotective effects[14,57,58,69]. Furthermore DM is associated with derangements in the regulation of intracellular calcium and elevated cytosolic calcium may have a role in the pathogenesis of complications in DM[91].

Hyperglycemia causes an acute rise in cytosolic calcium ($Ca^{2+}$) due to increased calcium influx and in certain cells to mobilization of intracellular calcium stores as well. The increase in calcium entry is secondary to the activation of calcium channels[91]. In animal diabetic models, treatment with verapamil normalizes cell $Ca^{2+}$ and prevents and/or reverses the resulting derangements in cellular function[91].

It has been found that verapamil prevents β-cell apoptosis in mouse models of type 1 and type 2 DM, enhances endogenous insulin levels and rescues mice from streptozotocin-induced DM[39].

Furthermore, also a cohort study, two randomized-controlled study and a systematic review with metanalysis show that verapamil seems to exert favorable effects on glycemic control in diabetic patients[40,41,43].

In addition, a recent randomized-controlled trial of lisinopril alone (an ACEI) or in combination with verapamil as a therapy for DN in Type 2 diabetic hypertensive patients with moderately increased albuminuria (UACR: 30-300 mg/g) showed that Lisinopril/Verapamil combination group significantly decreased fasting blood glucose, HbA1c, UACR, compared with the baseline levels ($p<0.001$ for all comparisons) and with Lisinopril monotherapy group ($p<0.001$)[92].

In summarize, verapamil, through its potential beneficial effects on glucose homeostasis, its antiproteinuric properties, its capacity to improve left diastolic function, its antihypertensive effect, its cardiac anti-ischaemic effects, and its sympathetic antagonist effect seems to potentially break the "vicious cycle" that lay the foundation for the development of CRS in diabetic hypertensive patients (Figure 2).

## Conclusions

Given its potential beneficial effects on blood glucose levels control, proteinuria, BP, IHD, SNS overactivity and LV diastolic function, verapamil may be considered as a potentially useful drug
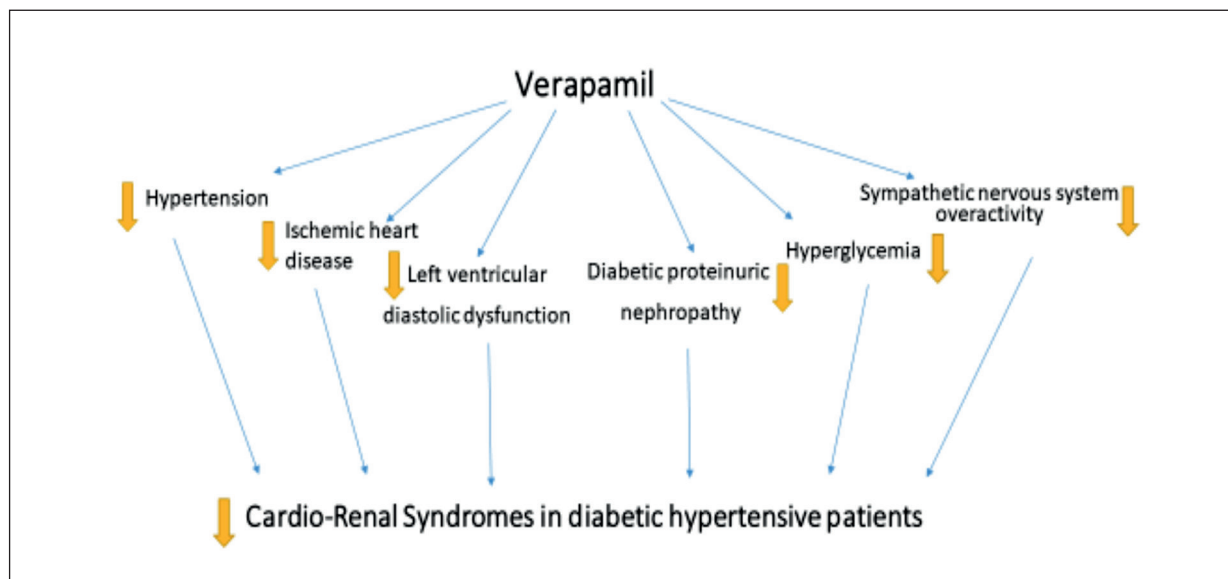


**Figure 2.** Effects of Verapamil in the prevention and treatment of Cardio-Renal syndromes.

in hypertensive patients with DM, HFpEF with or without ischemic heart disease and diabetic proteinuric nephropathy as when ACE inhibitors or ARBs are contraindicated and as in addition to administration of an ACE inhibitor or an ARB when these drugs fail to provide an adequate response.

## Conflict of Interest

## Acknowledgements

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