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**novel treatment approaches in hypertensive type two diabetic patients**

Castro Torres Y *et al*. novel treatment approaches for diabetics

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**Abstract**

Type 2 diabetes mellitus (T2DM) and hypertension represent two common conditions worldwide. Their frequent association with cardiovascular diseases makes management of hypertensive patients with T2DM an important clinical priority. Carvedilol and renal denervation are two promising choices to reduce plasma glucose levels and blood pressure in hypertensive patients with T2DM to reduce future complications and improve clinical outcomes and prognosis. Pathophysiological mechanisms of both options are under investigation, but one of the most accepted is an attenuation in sympathetic nervous system activity which lowers blood pressure and improves insulin sensitivity. Choice of these therapeutic approaches should be individualized based on specific characteristics of each patient. Further investigations are needed to determine when to consider their use in clinical practice.

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**Key words:** Diabetes mellitus; Carvedilol; Renal denervation; Insulin resistance; Glucose; Hypertension; Metabolic disorders; Ablation

**Core tip:** Type 2 diabetes mellitus and hypertension are two common conditions worldwide which increase the risk of cardiovascular disease with resulting disabilities and mortality. Carvedilol and renal denervation are two promising therapies to decrease insulin resistance and lower blood pressure by attenuating sympathetic nervous system activity. This review examines the clinical reports of these novel approaches.

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**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) and hypertension (HTN) represent two common conditions worldwide. They increase the risk for the development of cardiovascular diseases with adverse clinical outcomes including disabilities and mortality[1]. The International Diabetes Federation reports that diabetes kills one person every six seconds and afflicts 382 million people worldwide. The federation estimates that the number of people affected by the disease is expected to climb to 592 million by 2035[2].

DM is a group of metabolic diseases characterized by impairment in glucose, lipid and protein metabolism, resulting from alterations in insulin secretion, insulin action or both. While four types of DM have been classified, T2DM is the most prevalent and accounts for 90% to 95% of all diagnosed cases[3-6]. Its pathophysiology includes an increase in insulin resistance (IR) in tissues with subsequent relative insulin deficiency[7]. A great number of T2DM patients suffer from associated cardiovascular diseases. One of the most common is HTN. Over 60% of patients with T2DM have HTN[8] with resulting four-fold increased cardiovascular risk and death from complications[9,10].

Initial recommended treatment of HTN in patients with T2DM is angiotensin- converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). In the absence of cardiac comorbidity, traditional beta-blockers which increase IR do not constitute an initial choice for the treatment of HTN in patients with T2DM[4]. However, carvedilol which is a third-generation beta-blocker in some studies has demonstrated efficacy to reduce plasma glucose levels and IR[11-13] in patients with and without T2DM. Also in recent investigations, renal denervation (RDN) by catheter using radiofrequency energy has been associated with a decrease in IR in T2DM patients with an improvement in glucose control[14,15]. With both therapies the fall of plasma glucose concentrations and a reduction in blood pressure is likely due to an attenuation in sympathetic nervous system activity. Figure 1 reviews proposed antihypertensive mechanisms of carvedilol and RDN. These observations could open new choices to manage hypertensive T2DM patients with the use of one or both treatments. The benefit of improving patients´ blood pressure would be complemented with an IR reduction, decreasing significantly the risk of future complications.

In this article we will review studies which suggest that carvedilol and RDN improve glucose metabolism as well as lower blood pressure in hypertensive patients with T2DM.

**STUDIES THAT OBSERVED THAT CARVEDILOL IMPROVED GLUCOSE CONTROL IN HYPERTENSIVE PATIENTS WITH T2DM**

It is well recognized that traditional beta-blockers have negative effects on glucose and IR[16]. In contrast, studies have demonstrated that carvedilol stabilizes plasma glucose levels and decreases IR, suggesting a novel therapeutic option in hypertensive patients with T2DM.

Carvedilol is a third-generation, nonselective beta-blocker that also possesses alpha-1 adrenergic blocking, antioxidant and calcium antagonist properties. It is a racemic lipophilic aryloxypropanolamine that causes both precapillary vasodilatation and is devoid of intrinsic sympathomimetic activity[17-20]. Carvedilol is absorbed rapidly after oral administration and it is cleared by aromatic-ring oxidation and glucuronidation in the liver. Compared with traditional beta-blockers, carvedilol has the same pharmacological actions of reducing heart rate and blood pressure[21-23]. Due to these properties, carvedilol has been used in the treatment of heart failure[24,25], angina pectoris[26,27], to improve cardiac function after myocardial infarction[28] and to reduce infarct size following myocardial ischemia and reperfusion injury[29]. Carvedilol is indicated for treating patients with congestive heart failure and after myocardial infarction with ejection fractions less than 40 per cent because it has been shown to decrease mortality.

In general, traditional beta-blockers in hypertensive trials have been found to increase IR, facilitate weight gain and raise triglyceride levels. The metabolic benefits of carvedilol administration on plasma glucose reduction in patients with and without DM have been studied over many years and the results are summarized in Table 1 and discussed below.

Ehmer *et al*[30] conducted a study in non-insulin-dependent patients with DM with the aim to compare the antihypertensive effects and the influence on carbohydrate metabolism of carvedilol *vs* metoprolol tartrate. The results after eight weeks showed similar blood pressure reduction and in both groups plasma glucose concentrations remained within normal limits and glycated hemoglobin was unchanged.

Giugliano *et al*[12] compared the metabolic and cardiovascular effects of carvedilol *vs* atenolol in non-insulin-dependent T2DM hypertensive patients. Reduction in blood pressure was similar with carvedilol and atenolol, but the patients that received treatment with carvedilol had better metabolic responses. Over 24 wk, fasting plasma glucose, insulin and triglycerides levels decreased with carvedilol and increased with atenolol. In addition, an increase in high-density lipoprotein cholesterol level and decrease in lipid peroxidation was seen with carvedilol but not seen with atenolol. By improving glucose and lipid metabolism and reducing lipid peroxidation, the authors suggested that carvedilol may offer advantages in hypertensive patients with T2DM. The benefits of lipid reduction in high cardiovascular risk patients with DM have been demonstrated. In patients with DM the use of simvastatin resulted in a reduction in total mortality (43%), major coronary heart disease events (55%) and all atherosclerotic events (37%) and these reductions were greater than in non-diabetic patients[31]. In most guidelines, traditional beta-blockers are not recommended in hypertensive T2DM patients due to impairment in metabolic control and worsening lipid profile[4]. In contrast, carvedilol lowers blood pressure, improves glucose control and lipid profile, and, thus, is a unique choice in treating hypertensive T2DM patients.

An advance in this field was when researchers published the results of the GEMINI Trial which compared the glycemic and metabolic effects of carvedilol *vs* metoprolol tartrate in patients with HTN and T2DM already receiving renin-angiotensin system blockade[11].This was a randomized, double-blind study, carried out in 1235 participants. Patients were randomized to receive a 6.25 to 25 mg dose of carvedilol (*n* = 498) or 50 to 200 mg dose of metoprolol tartrate (*n* = 737), each twice daily in addition to renin-angiotensin system blockers to achieve blood pressure goal of 130/80 mmHg. After a follow up of 35 wk, the mean of glycosylated hemoglobin increased with metoprolol [0.15% (0.04%); *P* < 0.001] but not with carvedilol [0.02% (0.04%); *P* = 0.65]. Also an improvement of insulin sensitivity was seen with carvedilol (-9.1%; *P* = 0.004) but not with metoprolol tartrate (-2.0%; *P* = 0.48). This study supports the previous benefits observed with the use of carvedilol to improve glucose control in hypertensive patients with T2DM. Particularly in this work, carvedilol associated with simultaneous administration of renin-angiotensin system blockers was superior to metoprolol tartrate to achieve this objective. In patients with diabetes, traditional beta-blockers have been shown to increase fasting glucose, increase hemoglobin A1C, facilitate weight gain and increase triglycerides by approximately thirteen per cent. In the GEMINI Trial, hypertensive diabetic patients receiving renin-angiotensin system blockade and receiving carvedilol demonstrated stabilization of glycemic control, improvement of IR, less effect on triglycerides and less development of microalbuminuria. This study supports earlier investigations suggesting that carvedilol is uniquely different than traditional beta-blockers.

More recently an extension of the GEMINI investigation was published analyzing treatment differences in subgroups on glycemic control comparing carvedilol and metoprolol tartrate in diabetic hypertensive patients on renin-angiotensin system blockers[32]. Data analyses revealed that both carvedilol and metoprolol patients had significant and similar reductions in blood pressure. After adjustment for age there was a significant treatment benefit favoring carvedilol over metoprolol from change in baseline in glycosylated hemoglobin (0.022% *vs* 0.057%; *P* = 0.003) and IR (-9.09% *vs* -1.76%; *P* = 0.015). Female patients who received carvedilol were favored with a reduction in baseline glycosylated hemoglobin (-0.04% *vs* 0.16%; *P* = 0.003). In regard to race, carvedilol showed better results than metoprolol in African Americans patients from baseline in HOMA IR levels (-17.0% *vs* 8.2%, *P* = 0.01). The fact that carvedilol showed good blood pressure reduction and reduced glycosylated hemoglobin and IR in African American patients has important clinical implications. African Americans represent a special hypertensive group with a poor prognosis and with increased risk to develop additional complications, which are associated with the existence of frequent comorbidities and genetic predispositions[33-36]. African American T2DM hypertensive patients frequently have poor blood pressure responses to renin-angiotensin system blockers[37-39]. The GEMINI results suggest that carvedilol may be useful in the treatment of hypertensive African American patients with T2DM. Carvedilol has the potential of achieving better metabolic control, reducing blood pressure with few side effects, and improve clinical outcomes. This option needs further investigation, but this study should stimulate future work in these patients.

In further support for the unique properties of carvedilol, Kveiborg examined the effects of carvedilol and metoprolol tartrate on insulin-stimulated endothelial function in patients with T2DM[40]. These results also support the benefit of carvedilol compared with metoprolol observed in earlier studies. Treatment with carvedilol did not change insulin-stimulated endothelial function, whereas it deteriorated with metoprolol. IR is recognized as a pathophysiological cause of glucose disorders in patients with T2DM[7] and there are many reports about the relationship between this metabolic disorder and cardiovascular diseases[41,42]. Since traditional beta-blockers confer negative metabolic effects, carvedilol should be considered in the long term treatment of patients with cardiovascular disease[43-45].

Carvedilol also has been examined in the development of new onset of T2DM in patients with congestive heart failure. A total of 3029 patients with chronic heart failure were randomly assigned treatment with carvedilol or metoprolol tartrate. Fewer patients who received carvedilol were diagnosed with T2DM (119/1151 or 10.3%), compared to the metoprolol group (145/1147 or 12.6%) (Hazard ratio=0.78, CI 0.61 to 0.997; *P* = 0.048)[46]. The results suggest that T2DM and other metabolic disorders could be avoided or at least delayed with administration of carvedilol in patients at risk.

Another study evaluated the use of carvedilol in patients with systolic heart failure[47]. Carvedilol did not affect glycemic control in patients with T2DM and additionally it had a neutral effect on lipid profile and albuminuria status, confirming earlier observations.

Basat *et al*[48] studied 59 patients after a myocardial infarction to compare the effects of carvedilol *vs* metoprolol tartrate on IR and serum lipid. After 12 wk of treatment, carvedilol showed a significantly greater reduction in insulin, C-peptide, total cholesterol and triglyceride levels than metoprolol. The authors concluded than carvedilol could constitute an option to improve IR and lipid profile in patients after myocardial infarction. In patients with coronary artery disease and specifically in those after myocardial infarction, both poor glycemic control and lipid profile are well-known risk factors which increase the number of complications and impair the prognosis[49,50]. Choosing carvedilol in these high risk patients appears indicated because of its unique metabolic advantages compared to traditional beta- blockers.

**STUDIES THAT OBSERVED THAT RDN IMPROVED GLUCOSE CONTROL IN HYPERTENSIVE PATIENTS WITH T2DM**

RDN has emerged as a promising treatment for HTN[51-55]. Symplicity HTN-1[56] and HTN-2[57] studies demonstrated the efficacy and safety of RDN in patients with resistant HTN. State-transition modeling suggests that RDN is a cost-effective strategy for resistant HTN that can reduce the risk of stroke, myocardial infarction, coronary heart disease, heart failure and end-stage renal disease[58]. Another study suggests that potential lifetime cost-effectiveness ratios may be increased when RDN is performed earlier in patients with resistant HTN[59]. Follow-up of Symplicity patients demonstrate a durable blood pressure reduction out to 36 mo[60].

The principles of catheter-based RDN are based on the influence of afferent and efferent renal nerves in blood pressure physiopathology. As shown in Figure 1, after an ablation of renal nerves there is a reduction in blood pressure, sympathetic nervous system activity and renin-angiotensin system activity and increase in water and salt excretion[61].

Based on these observations, some investigators have examined catheter-based RDN on glucose control. Table 2 describes studies which observed glucose reduction after RDN. These studies were based on the knowledge that sympathetic overactivity can induce IR and hyperinsulinemia. Mahfoud *et al*[14] designed an investigation which enrolled 50 patients with resistant HTN. The group study (*n* = 37) received bilateral catheter-based RDN and the control group (*n* = 13) was assigned to continue medical therapy. Three months after treatment fasting glucose was reduced in the RDN group from 118 ± 3.4 to 108 ± 3.8 mg/dL (*P* = 0.039). Insulin levels were decreased from 20.8 ± 3.0 to 9.3 ± 2.5 µIU/mL (*P* = 0.006) and IR decreased from 6.0 ± 0.9 to 2.4 ± 0.8 (*P* *=* 0.001). Mean 2-h glucose levels during oral glucose tolerance testing were also reduced significantly by 27 mg/dL (*P* = 0.012) while there were no significant changes in BP or any of the metabolic markers in the control group. These excellent results in metabolic control were accompanied by a significant reduction in blood pressure. This was the first study proving the efficiency of RDN to reduce IR and improve glycemic control. RDN represents one of the most promising non pharmacological strategies to treat HTN, thus, the possibility observed in this research to reduce blood pressure and concomitant IR may open new options for patients.

Guidelines of some societies recommend that patients who receive RDN continue antihypertensive medical therapy after the procedure because the blood pressure often decreases slowly[62,63]. In this study it is suggested that the improvements seen in glucose control are due to a reduction in central sympathetic outflow after RDN. If further studies support this concept in patients with T2DM other conditions with IR like obesity merit study[64].

There is further support for the concept than RDN may benefit glucose control. Other investigators have examined the effects of RDN on blood pressure, sleep apnea course, and glycemic control in patients with resistant HTN and sleep apnea. RDN decreased blood pressure, attenuated sleep apnea severity and decreased two hour post prandial plasma glucose and glycosylated hemoglobin levels[65].

**PROPOSED MECHANISMS TO EXPLAIN A PLASMA GLUCOSE REDUCTION FROM CARVEDILOL AND RDN**

There are several mechanisms as shown in Figure 2 that may explain improved glycemic control with the use of carvedilol and RDN.

Traditional beta-blockers cause an increase in peripheral vascular resistance due to unopposed alpha vasoconstriction with resultant reduced glucose disposal to skeletal muscles and reduction in glucose uptake[66]. Carvedilol has alpha-1 blocker properties that causes vasodilatation and maintenance of blood flow to skeletal muscles. This difference may explain in part carvedilol's actions on glucose control compared to traditional beta-blockers.

Another mechanism by which carvedilol may improve glucose control is by reducing oxygen reactive species. T2DM is associated with endothelial dysfunction with increased reactive oxygen species and decreased endothelial nitric oxide synthase activity[67]. This phenomenon causes a reduction in oxide nitric availability with resultant vasoconstriction. Giuliano *et al*[12] found an increase in insulin sensitivity with a concomitant reduction in oxidative stress in patients with T2DM treated with carvedilol. Because carvedilol has antioxidant properties it appears to decrease reactive oxygen species and improve endothelial function. Other investigators have also found that carvedilol significantly reduced oxidative stress and C-reactive protein levels in hypertensive patients[68] and increased activity of antioxidant enzymes in diabetic rats[69].

On the other hand there are studies which have demonstrated that IR is related to an increase in sympathetic nervous system activation. An increase in sympathetic nerve activity and HTN in Caucasians with IR has been observed[70]. T2DM and HTN are known to be closely linked with increased sympathetic nervous activity and IR[71,72]. Reflex sympathetic activation has been shown to induce acute IR in the human forearm[73]. Carvedilol causes a significant reduction in cardiac and systemic norepinephrine spillover and this effect was not seen with other beta-blockers like metoprolol[74,75]. The relationship between an increase in sympathetic nervous activity and the development of IR, and the ability of carvedilol to reduce systemic norepinephrine may in part explain the findings of this drug reducing glucose levels. Similar results reducing norepinephrine spillover have been seen with the use of catheter-based RDN[56]. Increased sympathetic nervous system activity in tissues can result in IR. There is evidence of impaired ability of the cells to transport glucose through their membranes due to a decrease in blood flow after a rise in noradrenaline concentration[73]. The mechanism could be related to an increased distance that insulin has to travel from intravascular compartment to cell membranes due to a reduction of number of open capillaries as a consequence of vasoconstriction by sympathetic overactivity.

Another mechanism by which carvedilol may improve glucose control could be through the positive effects of carvedilol improving lipid profile. There appears to be a direct relationship between free fatty acids and IR. It is not fully understood why high plasma levels of fatty acids can produce IR, but a proposed mechanism is that permanent increases in plasma free fatty acids results in an intracellular accumulation of triglycerides and other compounds involved in triglyceride synthesis. Some of these compounds can activate a novel protein kinase C, and this protein is able to cause IR by decreasing tyrosine phosphorylation of the insulin receptor substrates[76-78]. Thus, the improvement in lipid profile observed with carvedilol[11,12] may in part explain, its ability to increase insulin sensitivity and subsequently improve glucose control.

Both carvedilol and RDN appear to reduce glucose levels by a decrease in IR and this change is associated with a reduction in sympathetic nervous system activity. However, beyond this possible relationship there are other possible mechanisms to explain improved glucose control after administration of carvedilol. Further investigations are needed to understand the metabolic pathways resulting in improved glucose control with the use of carvedilol and RDN.

**COMPARISON BETWEEN CARVEDILOL AND RDN TO REDUCE GLUCOSE LEVELS**

A comparison between carvedilol and RDN as options to reduce blood pressure and glucose levels in T2DM hypertensive patients is listed in Table 3. While carvedilol is administrated as an oral medication which requires patient's adherence, RDN is an interventional procedure whose safety and durability is still under investigation. Clinical trial data from Symplicity radiofrequency catheter systems have created much interest in the role of the renal nerves in HTN and other conditions such as diabetes mellitus. Furthermore, the attenuation of blood pressure observed has led to the rapid development of alternative methods of RDN by radiofrequency ablation as well as by ultrasound ablation and peri-vascular pharmacologic ablation. Many trials investigating these various innovative approaches to achieve RDN are ongoing. The factors which should be examined when considering carvedilol and/or RDN are the efficacy, safety and cost. Also, physicians need to individualize the recommended treatment because depending on physiological characteristics patient responses (and benefits) will vary.

**PERSPECTIVE**

Patients with HTN and T2DM require long term therapy. Thus, choice of antihypertensive agents results in long term risks and benefits. Initial recommended treatment of HTN in patients with T2DM is ACE inhibitors or ARBs which have favorable effects on carbohydrate metabolism and insulin resistance. Long-acting dihydropyridines have a neutral effect on glucose metabolism and insulin resistance. In contrast, thiazide-type diuretics can cause hyperglycemia and traditional beta-blockers can increase IR. Furthermore, hypertensive patients with increased cardiovascular risk may require 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, or statins, which appear (with the exception of pravastatin) to increase the risk of patients developing T2DM. Carvedilol and RDN appear to improve insulin sensitivity and glucose metabolism as well as lower blood pressure. Some guidelines recognize carvedilol's unique metabolic advantages compared to traditional beta-blockers and recommend its use in patients with HTN and T2DM if blood pressure goals have not been achieved using ACE inhibitors or ARBs. Carvedilol has been shown to stabilize HbA1c, improve insulin resistance, and slow development of microalbuminuria in the presence of renin-angiotensin system blockade compared with metoprolol tartrate[11].

Use of carvedilol should be individualized in patients with HTN and T2DM. In general, beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities. Furthermore, beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Presently RDN should only be considered in patients with resistant hypertension after causes of secondary hypertension have been excluded, with fairly preserved renal function and eligible renal arterial anatomy. It is not recommended to perform RDN in patients with HTN and T2DM outside of appropriately designed clinical trials.

**CONCLUSION**

Carvedilol and RDN improve glucose metabolism and insulin sensitivity in parallel with blood pressure reduction. These novel approaches may therefore provide benefit in patients with resistant HTN and T2DM who are at high cardiovascular risk and have not reached recommended goals to improve endothelial function and preserve renal function. An attenuation in sympathetic nervous system activity is the most likely mechanism to explain these actions. There have been no head-to-head comparisons, but RDN appears to have a greater effect on glucose metabolism than carvedilol. Further investigations and follow up are needed to determine the long-term durability of RDN, its efficacy in other diseases such as heart failure, stroke and kidney failure, and its use in stage 1 HTN. Currently, there are no clinical trial data available to indicate that RDN improves cardiovascular outcomes. If further trials confirm blood pressure lowering and improved glucose metabolism with carvedilol and RDN, these approaches represent reasonable choices for the treatment of patients with HTN and T2DM who have not reached guideline goals. These novel approaches could be used together to reach goals. Use of these novel treatments should be individualized in patients taking into account efficacy, safety, and cost.

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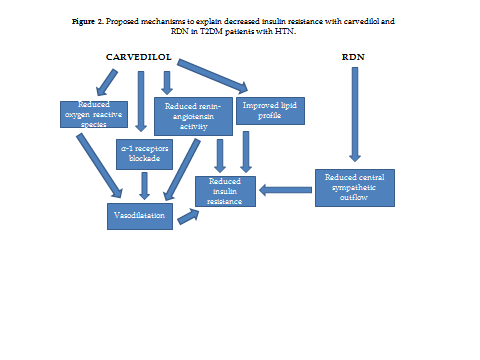
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**Figure 1 Antihypertensive mechanisms of carvedilol and renal denervation.**



**Figure 2 Proposed mechanisms to explain decreased insulin resistance with carvedilol and renal denervation in type 2 diabetes mellitus patients with hypertension.**

**Table 1** **Studies which observed glucose reduction carvedilol**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Study design** | **Participants** | **Main results** |
| Ehmer *et al*[30] | Prospective randomized open parallel group trial | 49 non-insulin-dependent diabetics with mild to moderate HTN (carvedilol  *n* = 25, metoprolol *n* = 24) | Blood glucose concentrations were maintained within narrow limits. Glycated haemoglobin A1 remained unchanged. There was a reduction in blood pressure in both groups |
| Giugliano *et al*[12] | Prospective single-blind randomized trial | 45 patients with non-insulin-dependent DM and HTN (carvedilol *n* = 23, atenolol *n* = 22) | Patients treated with carvedilol had improved glucose and lipid metabolism and reduced lipid perioxidation compared to atenolol. Both reduced blood pressure |
| Bakris *et al*[11] | Prospective double-blind randomized trial | GEMINI study, 1235 patients with HTN and T2DM (carvedilol *n* = 498, metoprolol tartrate *n* = 737) | The mean glycosylated hemoglobin increased with metoprolol, but not with carvedilol. An improvement of insulin sensitivity was seen with carvedilol but not with metoprolol |
| Phillips *et al*[32] | Prospective double-blind randomized trial | GEMINI study 1235 patients with HTN and T2DM (carvedilol *n* = 498, metoprolol tartrate *n* = 737) | After and adjustment for age carvedilol was superior than metoprolol reducing baseline glycosylated hemoglobin and also in female patients. In black people carvedilol showed a reduction in IR greater than metoprolol |
| Kveiborg *et al*[40] | Prospective randomized open parallel group trial | 19 patients with T2DM (metoprolol succinate *n* = 10, carvedilol *n* = 9) and 10 controls | Treatment with carvedilol did not change insulin-stimulated endothelial function, whereas it deteriorated with metoprolol |
| Torp-Pederse *et al*[46] | Prospective double-blind randomized trial | 3029 patients with chronic heart failure and T2DM (carvedilol *n* = 1511, metoprolol tartrate *n* = 1518) | Fewer patients treated with carvedilol developed T2DM than with metoprolol |
| Wai *et al*[47] | Observational cohort trial | 125 patients with T2DM and heart failure (carvedilol *n* = 80, bisoprolol  *n* = 45) | Carvedilol significantly improved glycemic control in subjects with heart failure and T2DM |
| Basat *et al*[48] | Prospective double-blind randomized trial | 59 patients with ST-elevation myocardial infarction (carvedilol *n* = 26, metoprolol *n* = 31) | After myocardial infarction, carvedilol added to background therapy improved insulin resistance and lipid profile |

T2DM: Type 2 diabetes mellitus; HTN: Hypertension.

**Table 2** **Studies which observed glucose reduction after renal denervation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Study design** | **Participants** | **Main results** |
| Mahfoud *et al*[14] | Prospective, controlled unblinded, randomized study | 50 patients with resistant HTN (37 patients underwent catheter-based RDN and 13 patients in a control group | RDN improved glucose metabolism and insulin sensitivity in addition to a significantly reducing blood pressure |
| Witkowski *et al*[65] | Prospective, nonrandomized, open-label study | 10 patients with refractory hypertension and sleep apnea (7 men and 3 women, who underwent RDN) | RDN reduced blood pressure and improved glucose metabolism |

HTN: Hypertension: RDN: Renal denervation.

**Table 3 Comparison between carvedilol and renal denervation as therapeutic choices to reduce blood pressure and glucose levels in hypertensive type 2 diabetes mellitus patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Therapeutic method** | **Mechanism of action** | **Medical indication** | **Mechanisms which explain glucose reduction** | **Contraindications** | **Side effects** |
| Carvedilol | α1, non-selective β-blocker, antioxidant and calcium antagonist properties[17-20] | Treatment of hypertension[21] heart failure[25] and coronary artery disease[27 ] | An improvement in insulin sensitivity by a reduction in sympathetic nerve activity [74,75] and free radicals[68,69] | Bronchial asthma, second-third degree atrioventricular block, sick sinus syndrome, severe bradycardia, patients with severe cardiogenic shock and heart failure who use inotropic drugs and hepatic impairement[17-20] | Frequent: edema, dizziness, bradycardia,  hypotension, nausea, diarrhea and blurred  vision  Rare: deterioration  of renal and hepatic function[17-20] |
| RDN | Ablation of afferent and efferent renal nerves[51-55] | Treatment of resistant hypertension[56,57] | An improvement in insulin sensitivity by reduction in sympathetic nerve activity56,57 | Polar or accessory arteries, renal artery stenosis, prior renal revascularization and glomerular filtration rate < 45 mL/min per 1.73m2 [56,57,62] | Renal artery dissection, postprocedural hypotension, femoral artery pseudoaneuryn, intraprocedural bradycardia56,57 |