World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v5.i4.536

World J Diabetes 2014 August 15; 5(4): 536-545
ISSN 1948-9358 (online)

REVIEW

Novel treatment approaches in hypertensive type 2 diabetic patients

Yaniel Castro Torres, Richard E Katholi

Yaniel Castro Torres, Facultad de Medicina, Universidad de Ciencias Médicas Dr. Serafín Ruiz de Zárate Ruiz, Santa Clara 50100, Villa Clara, Cuba
Richard E Katholi, Southern Illinois University School of Medicine and Prairie Cardiovascular Consultants, Springfield, IL 62701, United States
Author contributions: Castro Torres Y and Katholi RE were both involved in the design of the manuscript; both wrote major sections and both contributed to multiple revisions.
Correspondence to: Richard E Katholi, MD, Prairie Cardiovascular Consultants, Southern Illinois University School of Medicine and Prairie Cardiovascular Consultants, 619 E. Mason St., Ste.4P57, Springfield, IL 62701, United States. rkatholi@prairieheart.com
Telephone: +1-217-7880706 Fax: +1-217-7576502
Received: March 14, 2014 Revised: May 6, 2014
Accepted: June 10, 2014
Published online: August 15, 2014

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.

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.

Castro Torres Y, Katholi RE. Novel treatment approaches in hypertensive type 2 diabetic patients. *World J Diabetes* 2014; 5(4): 536-545 Available from: URL: http://www.wjgnet.com/1948-9358/full/v5/i4/536.htm DOI: http://dx.doi.org/10.4239/wjd.v5.i4.536

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 car-

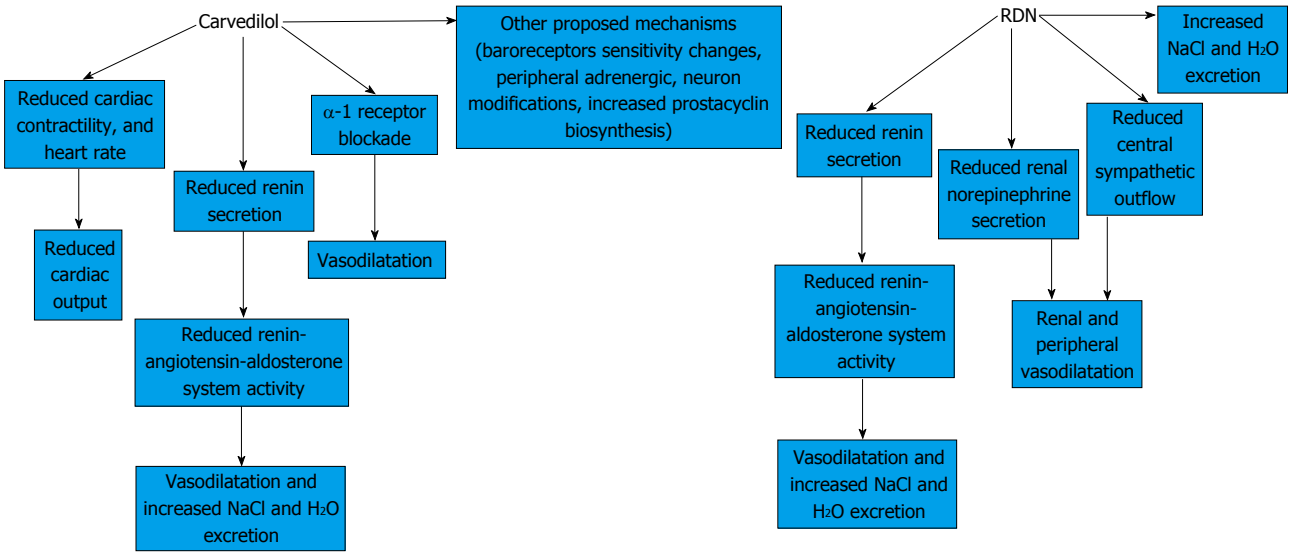

Figure 1 Antihypertensive mechanisms of carvedilol and renal denervation.

diovascular 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 percent 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 cardio-

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-Pedersen *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.

vascular 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 *et al*[40] examined the effects of carvedilol and metoprolol tartrate on insulin-stimulated endothelial function in patients with T2DM. 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%) (HR = 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

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.

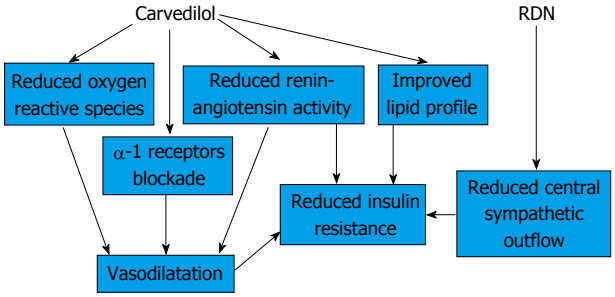

Figure 2 Proposed mechanisms to explain decreased insulin resistance with carvedilol and renal denervation in type 2 diabetes mellitus patients with hypertension.

(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. Giugliano *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

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 activity[56,57]	Polar or accessory arteries, renal artery stenosis, prior renal revascularization and glomerular filtration rate < 45 mL/min per 1.73 m^2[56,57,62]	Renal artery dissection, postprocedural hypotension, femoral artery pseudoaneuryn, intraprocedural bradycardia[56,57]

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.

REFERENCES

1 **Khavandi K**, Amer H, Ibrahim B, Brownrigg J. Strategies for preventing type 2 diabetes: an update for clinicians. *Ther Adv Chronic Dis* 2013; **4**: 242-261 [PMID: 23997928 DOI: 10.1177/2040622313494986]

2 International Diabetes Federation 2011. Global Burden: Prevalence and Projections, 2011 and 2030. Available from http://www.diabetesatlas.org/content/diabetes-and-impaired glucose-tolerance

3 **Go AS**, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013; **127**: 143-152 [PMID: 23283859 DOI: 10.1161/CIR.0b013e318282ab8f]

4 **Rydén L**, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, De Backer G, Sirnes PA, Ezquerra EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schächinger V, Scheen A, Schirmer H, Strömberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; **34**: 3035-3087 [PMID: 23996285 DOI: 10.1093/eurheartj/eht108]

5 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; **36** Suppl 1: S67-S74 [PMID: 23264425 DOI: 10.2337/dc13-S067]

6 **Maraschin Jde F**, Murussi N, Witter V, Silveiro SP. Diabetes mellitus classification. *Arq Bras Cardiol* 2010; **95**: e40-e46 [PMID: 20857049]

7 **Kahn SE**. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003; **46**: 3-19 [PMID: 12637977]

8 **Nilsson PM**, Cederholm J, Zethelius BR, Eliasson BR, Eeg-Olofsson K, Gudbj Rnsdottir S. Trends in blood pressure control in patients with type 2 diabetes: data from the Swedish National Diabetes Register (NDR). *Blood Press* 2011; **20**: 348-354 [PMID: 21675827 DOI: 10.3109/08037051.2011.587288]

9 **Mogensen CE**. New treatment guidelines for a patient with diabetes and hypertension. *J Hypertens Suppl* 2003; **21**: S25-S30 [PMID: 12769164]

10 **Haffner SM**, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339**: 229-234 [PMID: 9673301]

11 **Bakris GL**, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT, Oakes R, Lukas MA, Anderson KM, Bell DS. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; **292**: 2227-2236 [PMID: 15536109]

12 **Giugliano D**, Acampora R, Marfella R, De Rosa N, Ziccardi P, Ragone R, De Angelis L, D'Onofrio F. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. *Ann Intern Med* 1997; **126**: 955-959 [PMID: 9182472]

13 **Jacob S**, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens* 1996; **14**: 489-494 [PMID: 8761899]

14 **Mahfoud F**, Schlaich M, Kindermann I, Ukena C, Cremers B,

Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; **123**: 1940-1946 [PMID: 21518978 DOI: 10.1161/CIRCULATIONAHA.110.991869]

15 **Grassi G**. Renal denervation in cardiometabolic disease: concepts, achievements and perspectives. *Nutr Metab Cardiovasc Dis* 2013; **23**: 77-83 [PMID: 23149073 DOI: 10.1016/j.numecd.2012.09.004]

16 **Leonetti G**, Egan CG. Use of carvedilol in hypertension: an update. *Vasc Health Risk Manag* 2012; **8**: 307-322 [PMID: 22661898 DOI: 10.2147/VHRM.S31578]

17 **Sica DA**. Current concepts of pharmacotherapy in hypertension. Carvedilol: new considerations for its use in the diabetic patient with hypertension. *J Clin Hypertens* (Greenwich) 2005; **7**: 59-64 [PMID: 15655391]

18 **Frishman WH**. Carvedilol. *N Engl J Med* 1998; **339**: 1759-1765 [PMID: 9845712]

19 **Keating GM**, Jarvis B. Carvedilol: a review of its use in chronic heart failure. *Drugs* 2003; **63**: 1697-1741 [PMID: 12904089]

20 **Carter NJ**, Keating GM. Controlled-release carvedilol. *Am J Cardiovasc Drugs* 2008; **8**: 271-282 [PMID: 18690761]

21 **Stafylas PC**, Sarafidis PA. Carvedilol in hypertension treatment. *Vasc Health Risk Manag* 2008; **4**: 23-30 [PMID: 18629377]

22 **Morgan T**. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clin Pharmacokinet* 1994; **26**: 335-346 [PMID: 7914479]

23 **Beattie K**, Phadke G, Novakovic J. Carvedilol. *Profiles Drug Subst Excip Relat Methodol* 2013; **38**: 113-157 [PMID: 23668404 DOI: 10.1016/B978-0-12-407691-4.00004-6]

24 **Colucci WS**, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner-Bernstein JD, Young ST, Holcslaw TL, Lukas MA. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation* 1996; **94**: 2800-2806 [PMID: 8941105]

25 **Dickstein K**, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008; **10**: 933-989 [PMID: 18826876 DOI: 10.1016/j.ejheart.2008.08.005]

26 **van der Does R**, Hauf-Zachariou U, Pfarr E, Holtbrügge W, König S, Griffiths M, Lahiri A. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. *Am J Cardiol* 1999; **83**: 643-649 [PMID: 10080412]

27 **Brunner M**, Faber TS, Greve B, Keck A, Schnabel P, Jeron A, Meinertz T, Just H, Zehender M. Usefulness of carvedilol in unstable angina pectoris. *Am J Cardiol* 2000; **85**: 1173-1178 [PMID: 10801996]

28 **Dargie HJ**. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; **357**: 1385-1390 [PMID: 11356434]

29 **Brunvand H**, Liu G, Ma XL, Yue TL, Ruffolo RR, Feuerstein GZ. SB 211475, a metabolite of carvedilol, reduces infarct size after myocardial ischemic and reperfusion injury in rabbits. *Eur J Pharmacol* 1998; **356**: 193-198 [PMID: 9774249]

30 **Ehmer B**, van der Does R, Rudorf J. Influence of carvedilol on blood glucose and glycohaemoglobin A1 in non-insulin-dependent diabetics. *Drugs* 1988; **36** Suppl 6: 136-140 [PMID: 2908300]

31 **Pyörälä K**, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997; **20**: 614-620 [PMID: 9096989]

32 **Phillips RA**, Fonseca V, Katholi RE, McGill JB, Messerli FH, Bell DS, Raskin P, Wright JT, Iyengar M, Anderson KM, Lukas MA, Bakris GL. Demographic analyses of the effects of carvedilol vs metoprolol on glycemic control and insulin sensitivity in patients with type 2 diabetes and hypertension in the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study. *J Cardiometab Syndr* 2008; **3**: 211-217 [PMID: 19040589 DOI: 10.1111/j.1559-4572.2008.00017.x]

33 **Lip GY**, Beevers M, Beevers G. The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. *J Hypertens* 1994; **12**: 1297-1305 [PMID: 7868878]

34 **Stein CM**, Lang CC, Xie HG, Wood AJ. Hypertension in black people: study of specific genotypes and phenotypes will provide a greater understanding of interindividual and interethnic variability in blood pressure regulation than studies based on race. *Pharmacogenetics* 2001; **11**: 95-110 [PMID: 11266083]

35 **Baker EH**, Dong YB, Sagnella GA, Rothwell M, Onipinla AK, Markandu ND, Cappuccio FP, Cook DG, Persu A, Corvol P, Jeunemaitre X, Carter ND, MacGregor GA. Association of hypertension with T594M mutation in beta subunit of epithelial sodium channels in black people resident in London. *Lancet* 1998; **351**: 1388-1392 [PMID: 9593408]

36 **Hunte HE**, Mentz G, House JS, Schulz AJ, Williams DR, Elliott MR, Morenoff JD, White-Perkins DM. Variations in hypertension-related outcomes among Blacks, Whites and Hispanics in two large urban areas and in the United States. *Ethn Dis* 2012; **22**: 391-397 [PMID: 23140067]

37 **Chobanian AV**, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206-1252 [PMID: 14656957]

38 **Mancia G**, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281-1357 [PMID: 23817082 DOI: 10.1097/01.hjh.0000431740.32696.cc]

39 **Flack JM**, Sica DA, Bakris G, Brown AL, Ferdinand KC, Grimm RH, Hall WD, Jones WE, Kountz DS, Lea JP, Nasser S, Nesbitt SD, Saunders E, Scisney-Matlock M, Jamerson KA. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. *Hypertension* 2010; **56**: 780-800 [PMID: 20921433 DOI: 10.1161/HYPERTENSIONAHA.110.152892]

40 **Kveiborg B**, Hermann TS, Major-Pedersen A, Christiansen B, Rask-Madsen C, Raunsø J, Køber L, Torp-Pedersen C, Dominguez H. Metoprolol compared to carvedilol deteriorates insulin-stimulated endothelial function in patients with type 2 diabetes - a randomized study. *Cardiovasc Diabetol* 2010; **9**: 21 [PMID: 20500877 DOI: 10.1186/1475-2840-9-21]

41 **Cersosimo E**, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev* 2006; **22**: 423-436 [PMID: 16506274]

42 **Cleland SJ**, Petrie JR, Ueda S, Elliott HL, Connell JM. Insulin as a vascular hormone: implications for the pathophysiology of cardiovascular disease. *Clin Exp Pharmacol Physiol* 1998;

25: 175-184 [PMID: 9590566]
43 **Reiter MJ**. Cardiovascular drug class specificity: beta-blockers. *Prog Cardiovasc Dis* 2004; **47**: 11-33 [PMID: 15517513]
44 **Bangalore S**, Parkar S, Messerli FH. How useful are beta-blockers in cardiovascular disease? *Anadolu Kardiyol Derg* 2006; **6**: 358-363 [PMID: 17162285]
45 **Bangalore S**, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. *J Am Coll Cardiol* 2007; **50**: 563-572 [PMID: 17692739]
46 **Torp-Pedersen C**, Metra M, Charlesworth A, Spark P, Lukas MA, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Remme WJ, Scherhag A. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). *Heart* 2007; **93**: 968-973 [PMID: 17237130]
47 **Wai B**, Kearney LG, Hare DL, Ord M, Burrell LM, Srivastava PM. Beta blocker use in subjects with type 2 diabetes mellitus and systolic heart failure does not worsen glycaemic control. *Cardiovasc Diabetol* 2012; **11**: 14 [PMID: 22330091 DOI: 10.1186/1475-2840-11-14]
48 **Basat O**, Ucak S, Seber S, Oztekin E, Altuntas Y. After myocardial infarction carvedilol improves insulin resistance compared to metoprolol. *Clin Res Cardiol* 2006; **95**: 99-104 [PMID: 16598518]
49 **Heart Care Network Groups**. Current trends in lifestyle-related disease management by general practitioners: a report from the "Heart Care Network" groups. *J Atheroscler Thromb* 2009; **16**: 799-806 [PMID: 20032578]
50 **Doney AS**, Dannfald J, Kimber CH, Donnelly LA, Pearson E, Morris AD, Palmer CN. The FTO gene is associated with an atherogenic lipid profile and myocardial infarction in patients with type 2 diabetes: a Genetics of Diabetes Audit and Research Study in Tayside Scotland (Go-DARTS) study. *Circ Cardiovasc Genet* 2009; **2**: 255-259 [PMID: 20031593 DOI: 10.1161/CIRCGENETICS.108.822320]
51 **DiBona GF**, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**: R245-R253 [PMID: 19955493 DOI: 10.1152/ajpregu.00647.2009]
52 **Huan Y**, Cohen DL. Renal denervation: a potential new treatment for severe hypertension. *Clin Cardiol* 2013; **36**: 10-14 [PMID: 23124953 DOI: 10.1002/clc.22071]
53 **Mafeld S**, Vasdev N, Haslam P. Renal denervation for treatment-resistant hypertension. *Ther Adv Cardiovasc Dis* 2012; **6**: 245-258 [PMID: 23132232 DOI: 10.1177/1753944712468040]
54 **Castro Torres Y**, Katholi RE. Renal denervation for treating resistant hypertension: current evidence and future insights from a global perspective. *Int J Hypertens* 2013; **2013**: 513214 [PMID: 24369496 DOI: 10.1155/2013/513214]
55 **Castro Torres Y**. [Renal sympathetic denervation in resistant hypertension]. *Med Clin* (Barc) 2014; **142**: 45 [PMID: 23877099 DOI: 10.1016/j.medcli.2013.05.022]
56 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]
57 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]
58 **Geisler BP**, Egan BM, Cohen JT, Garner AM, Akehurst RL, Esler MD, Pietzsch JB. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol* 2012; **60**: 1271-1277 [PMID: 22981547 DOI: 10.1016/j.jacc.2012.07.029]
59 **Dorenkamp M**, Bonaventura K, Leber AW, Boldt J, Sohns C, Boldt LH, Haverkamp W, Frei U, Roser M. Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. *Eur Heart J* 2013; **34**: 451-461 [PMID: 23091202 DOI: 10.1093/eurheartj/ehs355]
60 **Krum H**, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; **383**: 622-629 [PMID: 24210779 DOI: 10.1016/S0140-6736(13)62192-3]
61 **Katholi RE**, Rocha-Singh KJ. The role of renal sympathetic nerves in hypertension: has percutaneous renal denervation refocused attention on their clinical significance? *Prog Cardiovasc Dis* 2009; **52**: 243-248 [PMID: 19917336 DOI: 10.1016/j.pcad.2009.09.003]
62 **Pathak A**, Girerd X, Azizi M, Benamer H, Halimi JM, Lantelme P, Lefevre T, Sapoval M. Expert consensus: Renal denervation for the treatment of hypertension. *Diagn Interv Imaging* 2012; **93**: 386-394 [PMID: 22560124 DOI: 10.1016/j.diii.2012.03.013]
63 **Mahfoud F**, Lüscher TF, Andersson B, Baumgartner I, Cifkova R, Dimario C, Doevendans P, Fagard R, Fajadet J, Komajda M, Lefèvre T, Lotan C, Sievert H, Volpe M, Widimsky P, Wijns W, Williams B, Windecker S, Witkowski A, Zeller T, Böhm M. Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. *Eur Heart J* 2013; **34**: 2149-2157 [PMID: 23620497 DOI: 10.1093/eurheartj/eht154]
64 **Soumaya K**. Molecular mechanisms of insulin resistance in diabetes. *Adv Exp Med Biol* 2012; **771**: 240-251 [PMID: 23393683]
65 **Witkowski A**, Prejbisz A, Florczak E, Kądziela J, Śliwiński P, Bieleń P, Michałowska I, Kabat M, Warchoł E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension* 2011; **58**: 559-565 [PMID: 21844482 DOI: 10.1161/HYPERTENSIONAHA.111.173799]
66 **Hansen O**, Johansson BW, Nilsson-Ehle P, Eklund B, Ohlsson I, Palenmark E, Pauler AM, Svensson K. Effects of carvedilol on the metabolic, hemodynamic, and electrocardiographic responses to increased plasma epinephrine in normal subjects. *J Cardiovasc Pharmacol* 1994; **24**: 853-859 [PMID: 7898065]
67 **Mehta JL**, Lopez LM, Chen L, Cox OE. Alterations in nitric oxide synthase activity, superoxide anion generation, and platelet aggregation in systemic hypertension, and effects of celiprolol. *Am J Cardiol* 1994; **74**: 901-905 [PMID: 7526676]
68 **Yasunari K**, Maeda K, Nakamura M, Watanabe T, Yoshikawa J, Asada A. Effects of carvedilol on oxidative stress in polymorphonuclear and mononuclear cells in patients with essential hypertension. *Am J Med* 2004; **116**: 460-465 [PMID: 15047035]
69 **Huang H**, Shan J, Pan XH, Wang HP, Qian LB. Carvedilol protected diabetic rat hearts via reducing oxidative stress. *J Zhejiang Univ Sci B* 2006; **7**: 725-731 [PMID: 16909474]
70 **Scherrer U**, Randin D, Tappy L, Vollenweider P, Jéquier E, Nicod P. Body fat and sympathetic nerve activity in healthy subjects. *Circulation* 1994; **89**: 2634-2640 [PMID: 8205675]
71 **Bikhazi AB**, Azar ST, Birbari AE, El-Zein GN, Haddad GE, Haddad RE, Bitar KM. Characterization of insulin-resistance: role of receptor alteration in insulin-dependent diabetes mellitus, essential hypertension and cardiac hypertrophy. *Eur J Pharm Sci* 2000; **11**: 299-306 [PMID: 11033073]
72 **Arauz-Pacheco C**, Raskin P. Hypertension in diabetes mellitus. *Endocrinol Metab Clin North Am* 1996; **25**: 401-423 [PMID: 8799706]
73 **Jamerson KA**, Julius S, Gudbrandsson T, Andersson O, Brant DO. Reflex sympathetic activation induces acute insu-

lin resistance in the human forearm. *Hypertension* 1993; **21**: 618-623 [PMID: 8491496]

74 **Kohno T**, Yoshikawa T, Yoshizawa A, Nakamura I, Anzai T, Satoh T, Ogawa S. Carvedilol exerts more potent antiadrenergic effect than metoprolol in heart failure. *Cardiovasc Drugs Ther* 2005; **19**: 347-355 [PMID: 16382297]

75 **Azevedo ER**, Kubo T, Mak S, Al-Hesayen A, Schofield A, Allan R, Kelly S, Newton GE, Floras JS, Parker JD. Nonselective versus selective beta-adrenergic receptor blockade in congestive heart failure: differential effects on sympathetic activity. *Circulation* 2001; **104**: 2194-2199 [PMID: 11684630]

76 **Boden G**, Lebed B, Schatz M, Homko C, Lemieux S. Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. *Diabetes* 2001; **50**: 1612-1617 [PMID: 11423483]

77 **Itani SI**, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. *Diabetes* 2002; **51**: 2005-2011 [PMID: 12086926]

78 **Yu C**, Chen Y, Cline GW, Zhang D, Zong H, Wang Y, Bergeron R, Kim JK, Cushman SW, Cooney GJ, Atcheson B, White MF, Kraegen EW, Shulman GI. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. *J Biol Chem* 2002; **277**: 50230-50236 [PMID: 12006582]

P- Reviewer: Hung MJ, Nakos G **S- Editor**: Song XX
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com