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Carvedilol can Replace Insulin in the Treatment of Type 2 Diabetes Mellitus

Anis Ahmad*

Unity Point Health Trinity Hospital, Rock Island, Illinois, USA

Abstract

Introduction: A large number of patients with diabetes mellitus do not want to take insulin or any injectable medication. Carvedilol can replace insulin in the treatment of T2 diabetes mellitus. Carvedilol alone or with oral anti-diabetic drugs (OAD) can replace the entire dose of insulin for patients with T2 diabetes (T2D). Carvedilol can replace insulin in patients on OAD who need insulin. Glycemic control was achieved in patients with T2D. This study was based on the hypothesis that carvedilol decreases insulin resistance, eliminates glucotoxicity and lipotoxicty and improves the function of beta-cell while reducing their apotosis.

Method: In this study, 48 patients with T2D were treated with carvedilol, which was an "off-label" use of carvedilol, for the treatment of diabetes mellitus. Twenty-nine patients with T2D were on OAD, and nineteen patients were taking insulin. Both groups had high HbA1c. Carvedilol was given with or without OAD to both groups, and glycemic control was achieved. OAD included metformin and/or glimepiride or glyburide and/or sitagliptin.

Results: Glycemic control was achieved using carvedilol with or without OAD in both groups.

Conclusion: 1. Carvedilol can reduce insulin resistance. 2. Carvedilol can replace insulin in patients with diabetes mellitus. 3. Carvedilol and metformin can prevent the progression of pre-diabetes to diabetes. 4. Patients who are on a very high dose of insulin can decrease that dose using carvedilol and metformin.

Keywords: Carvedilol; Diabetes mellitus Type 1 and 2; Insulin; Insulin resistance; Glucagon; Beta-cell; Glycemic control; Sympathetic nervous system

Abbreviations

T1D: Type 1 Diabetes Mellitus; T2D: Type 2 Diabetes Mellitus; OAD: Oral Anti-Diabetic Drugs; SNS:

Sympathetic Nervous System; HbA1c: Hemoglobin A1c; PSNS: Parasympathetic Nervous System

Introduction

Diabetes mellitus is at epidemic levels worldwide with no relief in sight [1-5]. Despite the numerous advances made in the treatment of diabetes mellitus, no oral drug thus far has been approved to reduce insulin resistance or replace insulin. The core problem in the pathogenesis of Type 2 diabetes mellitus (T2D) is insulin resistance, which principally involves liver muscles and adipose tissue [6-8].

Carvedilol is a beta-blocker that also improves insulin resistance, as shown by the GEMINI trial [9]. However, no further work has been conducted on insulin resistance and carvedilol since the GEMINI trial. Carvedilol acts by sensitizing insulin receptors that belong to tyrosine kinase receptors [10,11]. Metformin and TZD also act by sensitizing insulin receptors [12]. Carvedilol blocks beta 1, beta 2 and alpha-adrenergic receptors and does not affect blood levels of LDL, HDL or triglycerides. Carvedilol is an anti-inflammatory and antioxidant agent [13-16].

When used in the treatment of diabetes mellitus, carvedilol increases insulin secretion, decreases the secretion of glucagon, and improves the function, proliferation and regeneration of beta cells as well as decreases their apoptosis [5,6,7,17]. Carvedilol acts on the sympathetic nervous system (SNS), which is overstimulated in diabetes mellitus, and the SNS works in tandem with the parasympathetic nervous system (PSNS) [18-20].

In the practice of medicine, two types of patients with diabetes mellitus are encountered, and no treatments are available for any of these patients. The first group of patients are insulin dependent and refuse to take insulin or any injectable medications because of cost or inconvenience but have high HbA1c. The second group of patients are on the maximum dose of OAD with high HbA1c and require insulin or an injectable medication; however, they refuse to take injectable medication.

In this study, carvedilol was used, with or without OAD, to replace insulin or to reduce high doses of insulin and achieve glycemic control. This application is an "off-label" use of carvedilol [21]. The records of the patients who participated in this study were reviewed and are presented in this study. The OAD used in combination with carvedilol were metformin and/or glimepiride or glyburide and/or sitagliptin.

The mechanism of action of carvedilol in increasing insulin secretion is briefly described herein [12,22-24]. Carvedilol blocks the sympathetic nervous system, SNS, which is very important in insulin resistance and has been studied extensively. The SNS is overstimulated

***Corresponding author:** Anis Ahmad, Affiliated with Unity Point Health Trinity Hospital, Rock Island, Illinois. USA, Tel: 3097626161; Fax: 3097625387; E-mail: aahmad1950@gmail.com

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in diabetes mellitus due to hyperglycemia, high insulin levels, high free fatty acid levels, and high leptin levels in the blood but not due to high levels of glucagon in the blood. These abnormal changes are due to insulin resistance [25].

High insulin levels are seen in early stages of T2D, and as a result of insulin resistance, these high insulin levels decline over a period of time. Hyperglycemia is caused by high levels of glucagon with the overproduction of glucose. Hyperglycemia is also due to insulin resistance [26]. Hyperglycemia and high levels of free fatty acids cause the chronic glucotoxicity and chronic lipotoxicity of beta cells, leading the beta cells to become dysfunctional.

SNS overstimulation increases the secretion of glucagon by the alpha cells of the pancreas. SNS stimulation decreases insulin secretion by the pancreas [15,24,27]. SNS overstimulation causes gluconeogenesis, glycogenolysis, and lipolysis. High levels of glucagon increase gluconeogenesis in the liver and lipolysis and glycogenolysis [28]. These changes cause chronic hyperglycemia and chronic high free fatty acid levels in the blood [11,29].

An overactive SNS decreases glucose uptake by muscle mass due to vasoconstriction, but there is also an increase in the lipid content of cells of muscles, and both of these factors increase insulin resistance. There is an increase in lipolysis in adipose tissue due to overactive SNS and TNF alpha, which is an important aspect of insulin resistance. Norepinephrine and epinephrine are the main neurotransmitters for the SNS [30].

The aforementioned actions of the SNS are blocked by carvedilol while improving insulin secretion and blunting the action of glucagon [24,26]. Therefore, carvedilol has two actions on glucagon: decreasing its secretion and blunting its action [26]. By decreasing the secretion of glucagon, carvedilol not only decreases gluconeogenesis in the liver but also decreases glycogenolysis and lipolysis, eliminating chronic glucotoxicity and chronic lipotoxicity in beta cells and muscle cells [8,11]. Carvedilol, a beta-blocker, decreases gluconeogenesis in the liver [12]. Vasodilatation in muscles produced by carvedilol improves glucose uptake. The GLUT4 system is stimulated by insulin, which becomes active as insulin resistance decreases and more insulin is secreted [12,29]. Blockage of the SNS by carvedilol eliminates chronic glucotoxicity and chronic lipotoxicity, decreasing insulin resistance and improving the function of beta cells. This action facilitates insulin secretion and decreases the apoptosis of beta cells [5,6]. The mechanism is described above.

The PSNS and the SNS act in a fine balance with respect to each other. The PSNS is activated if the SNS is blocked by carvedilol, increasing the secretion of insulin by the release of acetylcholine and neuropeptides such as VIP, PACAP and GRP [7]. The stimulation of the SNS releases gelanin and NPY; these two neuropeptides decrease insulin secretion and increase the secretion of glucagon. These SNS actions are blocked by carvedilol; therefore, there is no decrease in the secretion of insulin [7]. The incretin hormones increase insulin secretion as insulin resistance decreases; improve beta cell function, proliferation, and neogenesis; and decrease beta cell apoptosis [6,10]. Carvedilol works on the kidneys and reduces microalbuminuria and insulin resistance in patients with diabetes mellitus. Inflammatory markers such as interleukin and tumor necrosis factor are affected by the tone of the SNS, which is blocked by carvedilol [18,30].

Materials and Methods

The use of carvedilol in this study was in line with the Food and Drug Administration (FDA) regulations stipulating that a drug can be used off label in the practice of medicine [31,32].

This study was non-funded and was carried out in an internal medicine clinic that also practices clinical cardiology and diabetes mellitus. Forty-eight patients were treated for a period of five months, their records were reviewed, and the results presented in this paper.

The estimation of insulin resistance and blood levels of insulin, glucagon, and epinephrine or nor-epinephrine was not performed, as this was a non-funded study. We hope this study will be followed by a trial to prove the findings documented herein. In this study, all 48 patients were diagnosed with T2D. The treatment included carvedilol alone or in combination with OAD. OAD consisted of metformin and/or glimepiride or glyburide and/or sitagliptin [33]. The glycemic control was defined as a fasting blood glucose less than 130 mg/dl and a postprandial blood sugar less than 180 mg/dl and HbA1c of 7.0 or less [21]. At the start of the study, all patients were examined and comprehensive blood work was done, including HbA1c.

The patients were divided in two groups based upon insulin-dependent status, and their records were observed. For all groups, HbA1c was evaluated after the complete withdrawal of insulin and after glycemic control was achieved. After glycemic control was achieved, comprehensive blood work was performed again.

Group 1 consisted of 19 patients of uncontrolled T2D who were insulin dependent with high HbA1c and who did not want to take insulin or any injectable medication. Carvedilol was added with/without OAD, replacing the entire dose of insulin. Glycemic control was achieved. Carvedilol alone was used in only one patient.

Group 2 consisted of 29 patients with uncontrolled T2D who were on the maximum dose of OAD with high HbA1c. These patients could not afford insulin or refused to take it or any injectable medications. Carvedilol was added to the existing therapy of OAD, and glycemic control was achieved. Carvedilol alone was used in three patients in this group (Tables 1 and 2).

None of the patients had experienced any significant or permanent weight loss since they were diagnosed with diabetes mellitus. The patients did not want to change their exercise program or lifestyle. All patients were given instructions for a diet program such as that advised

	Group 1 (n=19)	Group 2 (n=29)
Gender		
Male	6 (32%)	14 (48%)
Female	13 (68%)	15 (52%)
Age		
Average	63.2 yrs	66.9 yrs
Range	42-89 yrs	44-92 yrs

Table 1: Age and gender distribution by group

	Group 1 Average	Group 2 Average	P-value Across Groups
Initial HbA1c	9.24	9.07	0.2060
Final HbA1c	6.84	6.76	0.5579
HbA1c Change	2.39	2.31	0.4224
P-value Change	<0.00001	<0.00001	

Table 2: Comparison of average initial and final HbA1c values and change in HbA1c across groups.

by the ADA. All patients were instructed to check their blood sugar twice per day. The results were reviewed on each visit along with further discussion of diet. The side-effects of carvedilol were also discussed with all patients; side-effects include but are not limited to low blood pressure and slow pulse. Hypoglycemia was discussed with each patient as well. All patients who were on insulin knew how to take insulin and how to store it due to prior instruction in the use of insulin. Informed consent was obtained from each patient.

Exclusion criteria included patients with unstable angina, hypotension, atrioventricular block, or any arrhythmia other than atrial fibrillation. Patients with atrial fibrillation were allowed in the study because carvedilol can control atrial fibrillation. Patients with a history of acute myocardial infarction or acute cerebrovascular accident (CVA) in the previous year, those with chronic obstructive pulmonary disease or pulmonary fibrosis as well as current smokers were also excluded [12]. For all groups, the starting dose of carvedilol was 6.25 mg given every 12 h or 12.5 mg given every 12 h. The dose was increased every two weeks until the maximum dose of carvedilol, 25 mg every 12 h, was achieved.

Other medications used in combination with carvedilol included metformin, glyburide, and glimepiride or sitagliptin were added on an "as needed" basis to achieve glycemic control. The records of the treatment were reviewed at each patient visit. In Group 1, carvedilol with or without OAD decreased the patients' blood sugar to 130 mg/dl. In patients who were insulin dependent, the dose of insulin was decreased gradually until it was stopped.

The following data was extracted from the patients' records: age, gender, type of diabetes, insulin dosage and oral medications. Additionally, HbA1c was added before and after the initiation of carvedilol for glycemic control. Analysis was then carried out using the t-test for dependent means (pre/post-HbA1c) as well as Fisher's exact test and unpaired t-tests to assess similarity across groups (age, gender, HbA1c levels). Significance was set at $p<0.05$, and single-tailed tests were used for pre/post-HbA1c assessment.

Results

Patients in group 1

The use of insulin was completely eliminated. The highest dose of insulin at the start of the study period was 180 units per day. Insulin was replaced by carvedilol alone or with OAD. Glycemic control was achieved (Table 3).

Patients in group 2

Patients were on OAD, and carvedilol was added to their OAD regime instead of insulin. The patients in this group did not want to use insulin or could not afford insulin. Glycemic control was achieved (Table 4).

This descriptive study reviewed patient data for two groups of patients. Group 1 consisted of 19 insulin-dependent T2 diabetics. Group 2 consisted of 29 non-insulin-dependent T2 diabetics. The age and gender distributions of the two groups did not differ significantly ($p=0.2483$ and $p=0.3703$ respectively (Table 1).

In Group 1 (insulin-dependent diabetics), the average initial insulin dosage was 77.5 units per day. Insulin was eliminated in all patients in this group. The average initial HbA1c in Group 1 was 9.24. The average final HbA1c was 6.84, a reduction of 2.39 (23.87%) from the initial measurement. This difference represents a statistically significant reduction in HbA1c ($p<0.00001$). None of the patients in Group 1 were initially on oral medications. With the elimination of insulin in all 19 of the Group 1 patients, the average patient was on three oral medications (including carvedilol) at the time of final assessment.

In Group 2 (non-insulin-dependent diabetics), patients were, on average, taking two oral medications at the start of the time period with the average rising to three medications with the addition of carvedilol. Three patients were initially on no oral medications. The average initial HbA1c in Group 2 was 9.03. The average final HbA1c was 6.73, a reduction of 2.30 (24.24%) from the initial measurement. This difference represents a statistically significant reduction in HbA1c ($p<0.00001$).

Between-group HbA1c comparisons were conducted using unpaired t-tests. The results indicated that the average values for the two groups did not differ significantly with regard to initial or final HbA1c measurements nor was there a significant difference between groups with regard to the change in HbA1c pre/post-carvedilol (Table 2). Two patients dropped out of the study and are not included in the data presented here. The first patient lost interest in the study, while the second patient could not tolerate beta-blockers.

Discussion

The records of patients in Groups 1 and 2 show that if used alone or with oral anti-diabetic medications, the beta-blocker carvedilol is as effective as insulin and can replace insulin entirely and achieve glycemic control. In Group 1, the highest dose of insulin replaced was 180 units. Insulin was secreted by the pancreas of the patient, and glycemic control was achieved in T2D [9,28].

In Group 2, patients with T2D on OAD with high HbA1c did not have to use insulin, and the addition of carvedilol achieved glycemic control. Insulin, which was needed to achieve glycemic control, was secreted by the pancreas [9,28]. Carvedilol alone achieved glycemic control in only 3 patients with T2D.

According to this study, an increasing number of patients are demanding oral medications because of the inconvenience and cost of insulin or other injectable medications. Carvedilol with or without OAD can be an alternative treatment. This treatment was also used for the two groups of patients described in the introduction, all of whom were untreatable.

The replacement of 180 units of insulin in one patient, along with replacement of significant quantities of insulin in the other 47 patients, can occur only if there is an elimination or very significant reduction of insulin resistance. Furthermore, these results can only be achieved if there is significant improvement in the beta cell function and the replacement of beta cell mass [2,5,6,10]. The PSNS is involved in the proliferation of beta cells. Carvedilol blocks the SNS and stimulates the PSNS. The replacement of insulin in all patients occurred over a period of five months. A trial is needed to confirm these findings.

The endocrine pancreas has a significant remodeling capacity that plays a crucial role in the maintenance of glucose homeostasis. Changes in beta cell apoptosis, replication and size and islet neogenesis contribute to the remodeling of the endocrine pancreas [9]. According to the data analyzed, insulin secretion by the pancreas is restored after five months, but the destruction of beta cells by antibodies or other agents takes several years. The role of antibodies has no significance, as the beta cells that are not destroyed can be replaced within five months using carvedilol with OAD. In patients with long-term T2D, there is

Name	Age	Gender	Dose Of Insulin	Initial A1c	Final A1c	Percentage Reduction Of A1c	Final Medications
IDDM1	53	F	180 Units	11.9	6.6	44.5%	Carvedilol and metformin
IDDM2	42	F	130 Units	10.8	8.7	19.4%	Carvedilol, metformin, and glyburide micro
IDDM3	65	F	130 Units	7.3	6.4	12.3%	Carvedilol and glyburide micro
IDDM4	51	M	102 Units	9.1	8.5	6.6%	Carvedilol, metformin, glimepiride, and Januvia
IDDM5	69	F	100 Units	10.2	6.1	40.2%	Carvedilol and glyburide micro
IDDM6	54	F	90 Units	7.8	7.4	5.1%	Carvedilol, metformin, glimepiride, and Januvia
IDDM7	81	F	80 Units	7.6	6.5	13.3%	Carvedilol and glyburide micro
IDDM8	51	F	80 Units	10.3	6.0	41.8%	Carvedilol and glyburide micro
IDDM9	65	M	65 Units	9.0	5.5	38.9%	Carvedilol, metformin, and glyburide micro
IDDM10	65	F	56 Units	9.6	6.3	34.4%	Carvedilol, metformin, and glyburide micro
IDDM11	57	F	50 Units	13.6	7.3	46.3%	Carvedilol, metformin, and glyburide micro
IDDM12	72	F	40 Units	8.5	7.1	16.5%	Carvedilol and metformin
IDDM13	54	F	64 Units	7.8	7.1	8.9%	Carvedilol and metformin
IDDM14	71	M	50 Units	7.0	7.0	0%	Carvedilol
IDDM15	66	M	90 Units	9.3	6.8	26.9%	Carvedilol, metformin, and glyburide micro
IDDM16	89	F	40 Units	8.4	7.1	15.5%	Carvedilol and glucophage
IDDM17	45	F	80 Units	10.0	6.0	40.0%	Carvedilol, glimepiride, and metformin
IDDM18	72	M	6 units	8.4	7.1	15.5%	Carvedilol, metformin, and glimepiride
IDDM19	72	M	40 Units	9.01	6.54	27.4%	Carvedilol, metformin, and glimepiride

Table 3: Group 1: Insulin-dependent patient characteristics, medications, & comparison of A1C values pre/post addition of Carvedilol.

an extensive loss of beta cells, but there is evidence that some insulin is secreted and that insulin resistance occurs [27]. If the regeneration of beta cells can be achieved and if beta cell mass can be returned to normal by carvedilol and metformin with or without using other OAD, then the treatment of diabetes mellitus becomes much easier [5-7].

In pre-diabetic patients with T1D and T2D, carvedilol and metformin can be used to prevent prediabetes from progressing to fully diagnosed diabetes. If proven accurate by a trial, then T1D can even be prevented.

Anderson et al. [22] used carvedilol to maintain glycemic control in patients with hypertension and T2D [23]. The GEMINI trial compared the effects of metoprolol and carvedilol in patients with diabetes mellitus and hypertension. This study showed that carvedilol improves insulin resistance [19]. Carvedilol and metformin have some common pharmacological actions. Metformin increases the sensitivity of insulin receptors, decreases gluconeogenesis and increases glucose uptake in the muscle mass through GLUT4; metformin therefore blunts the action of glucagon [28].

The morbidity and mortality of CVD have remained high in patients with diabetes mellitus despite all the advances made in the last two decades. Beta-blockers are used to reduce cardiovascular morbidity and mortality, but they increase insulin resistance, increase the level of triglycerides and lower the level of HDL in patients with diabetes mellitus [20]. Carvedilol is a third-generation beta-blocker that lowers insulin resistance, does not affect lipid levels, is anti-inflammatory and is also an antioxidant. Subsequent trials may show whether the morbidity and mortality of CVD can be reduced further in patients with diabetes mellitus using carvedilol. Carvedilol is very cost effective and is used all over the world for the treatment of hypertension and CVD [24].

The research on oral insulin has not progressed much because the technology for the delivery of oral insulin from the bowel to blood has not been perfected. Oral insulin encounters insulin resistance in the blood and an overactive SNS; together, these two factors interfere with the action of oral insulin.

If oral insulin is absorbed in adequate amounts and administered with carvedilol, then insulin resistance will decrease, SNS will be blocked, and more insulin will be secreted by the pancreas. Oral insulin in combination with more insulin secreted by the pancreas should be as effective as injectable insulin, which will lead to the early approval of oral insulin by the FDA.

The data shows quite clearly that carvedilol alone or in combination with OAD can replace insulin, even in patients on high doses who refuse to take insulin. A trial can be conducted, and if these data are proven accurate, then the progression of both types of diabetes mellitus can be prevented [22].

Conclusion

1. The use of carvedilol as a drug for reducing insulin resistance requires approval from the FDA.
2. Carvedilol with or without OAD is as effective as insulin and can replace the entire dose of insulin.
3. Patients with T2D on oral medication with high HbA1c who refuse to take insulin can achieve glycemic control if carvedilol is added to their OAD regime.
4. The combination of carvedilol and oral insulin should be as effective as injectable insulin, leading to the early approval of oral insulin by the FDA.
5. Pre-diabetic patients can be treated with carvedilol and metformin to prevent their progression to diabetes mellitus.

NAME	AGE	GENDER	OAD	INITIAL A1C	WITH CARVEDILOL	FINAL A1C	PERCENTAGE REDUCTION IN A1C
NIDDM1	70	M	None	8.0	Carvedilol	6.1	23.8%
NIDDM2	54	F	Glimepiride, Metformin & Sitagliptin	8.0	Carvedilol	7.0	12.5%
NIDDM3	46	F	Glyburide Micro & Metformin	8.5	Carvedilol	7.6	10.6%
NIDDM4	76	M	Glyburide Micro	8.5	Carvedilol	6.5	23.5%
NIDDM5	75	M	Glimepiride and Sitagliptin	7.2	Carvedilol	6.6	8.3%
NIDDM6	56	M	Sitagliptin, Metformin & Glimepiride	9.5	Carvedilol	6.5	31.6%
NIDDM7	65	F	Glyburide Micro, Sitagliptin, & Metformin	8.5	Carvedilol	6.5	23.5%
NIDDM8	61	F	Metformin	8.6	Carvedilol	6.4	25.6%
NIDDM9	76	F	None	8.9	Carvedilol	6.1	31.5%
NIDDM10	84	M	Glimepiride & Metformin	8.5	Carvedilol	7.2	15.3%
NIDDM11	74	F	Glimepiride & Metformin	9.9	Carvedilol	7.3	26.3%
NIDDM12	60	M	Glimepiride & Metformin	11.5	Carvedilol	6.6	42.6%
NIDDM13	74	F	Metformin	8.2	Carvedilol	7.6	7.3%
NIDDM14	78	M	Metformin	8.7	Carvedilol	6.1	29.9%
NIDDM15	72	M	Glimepiride and Metformin	8.9	Carvedilol	6.6	25.8%
NIDDM16	66	F	Glimepiride	11.3	Carvedilol	7.6	32.7%
NIDDM17	60	M	Glimepiride and Metformin	8.5	Carvedilol	6.3	25.9%
NIDDM18	66	F	Glimepiride and Metformin	11.5	Carvedilol	7.2	37.4%
NIDDM19	72	F	Metformin	8.5	Carvedilol	6.3	25.9%
NIDDM20	56	F	Metformin	9.4	Carvedilol	6.6	29.8%
NIDDM21	71	F	Metformin	7.9	Carvedilol	6.7	15.9%
NIDDM22	56	M	None	9.7	Carvedilol	6.3	35.1%
NIDDM23	61	M	Glimepiride, Metformin, and Januvia	9.9	Carvedilol	7.2	27.3%
NIDDM24	52	F	Metformin	7.4	Carvedilol	7.4	0%
NIDDM25	87	F	Glimepiride and Januvia	9.3	Carvedilol	7.1	23.7%
NIDDM26	44	M	Metformin	10.0	Carvedilol	5.6	44.0%
NIDDM27	70	M	Glimepiride and Metformin	7.8	Carvedilol	7.7	1.3%
NIDDM28	92	F	Tradjenta	8.0	Carvedilol	6.4	20.0%
NIDDM29	67	M	Metformin	11.3	Carvedilol	6.0	46.9%

Table 4: Group 2: Non-insulin-dependent patient characteristics, medications, & comparison of A1C values pre/post addition of Carvedilol.

6. Cardiovascular morbidity and mortality can be reduced in patients with diabetes mellitus if carvedilol is used.

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Conflict of Interest

None.

Ethics in Publishing

"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet. Carvedilol was used off-label in the practice of medicine. Please see the reference herein: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.

Submission Declaration

The attached study has not been published previously as an abstract or as an article and is not under consideration for publication elsewhere. Its publication is approved by the author. If accepted, the attached study will not be published in the same form elsewhere, including electronically, in English or in any other language without the written consent of the copyright holder.

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