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HYPERTENSIVE HEART DISEASE: BENEFIT OF CARVEDILOL IN HEMODYNAMIC, LEFT VENTRICULAR RE-MODELING AND SURVIVAL

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Abstract:

The study objective was to discover if carvedilol enhanced constructive and functional variations in the left ventricle and decreased mortality within patients with hypertensive heart disease.

The parameters of echocariography, blood pressure, heart rate, and research variables were evaluated pre and post therapy with carvedilol in 98 qualified patients.

At a median 50 milligram dose per day, carvedilol, in between the period of treatment in hypertensive heart disease reduced blood pressure level 10/10 mmHg, heart rate 10 beats/min, enhanced left ventricular ejection fraction from standard to follow-up (median: 6 years) (36%–47%)) and decreased left ventricular end-diastolic and end-systolic proportions (62 vs 56 mm; 53 vs 42 mm, respectively, all p-values <0.01). Left ventricular ejection fraction enhanced in sixty-nine percent patients. Similarly, patients who actually lacked enhanced left ventricular ejection fraction had almost six-fold greater mortality as opposed to those that enhanced (related risk; 5.7, 95% confidence interval: 1.3–25, p = 0.022).

Carvedilol decreased cardiac dimensions and enhanced left ventricular ejection fraction and cardiac renovating in patients with hypertensive heart disease. These types of treatment-related variations possessed an advantageous impact on the rate of survival.

Keywords: *Left ventricular reverse remodeling, beta-blockers, hypertensive heart disease, ejection fraction, survival.*

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INTRODUCTION:

Mortality rate deviate according to the heart failure severity, varying from 50% in five years around individuals with moderate disease to as much as 50% at one year when it comes to those with higher level heart failure (HORI, 2016).

The influence of beta-blockers on incidence and death-rate caused by heart failure with assorted etiologies remains confirm in large studies. Contrary renovating from the left ventricle could happen more or less often as per the etiology of heart failure. Cardiac transforming contains structural and workable variations of cardiac muscle, interstitium, and vessels that reflect genetic, electric, and portable aspects. Hypertension is a vital provocation to cardiac remodeling. Cardiac adjustments from hypertension exhibits hemodynamic excess, ischemia, neuro-humoral modifications, and stimulation of inflammatory cytokines. In concert, these adjustments can result in hypertensive heart disease (HHD). The clinical symptoms of HHD consist of left ventricular (LV) hypertrophy, myocardial ischemia, arrhythmia, and heart failure (HF) (James, 2016).

HF is more frequent in elderly people with a prevalence of 11.5% in the global population (⩾80 years). Hypertension, whilst the exclusively risk element, is in charge of roughly 4% of HF among adults in the world and an identical incidence of HF in Europe and Asia, although hypertension in collaboration with various other risk factors forego HF in 75% of patients. Left ventricular hypertrophy (LVH) by echo-cardiography is actually a frequent identifying in hypertensive field, additionally; the frequency improves using the severity of hypertension. Hypertensive issues with diagnostic HF could introduce along with conserved (⩾50%), mid-range (40%–49%), and decreased (<40%) ejection fraction (EF). Anti-hypertensive therapy can easily enhance LVH and decrease HF in hypertensive patients. Recently, issue has been brought up on whether antihypertensive treatment could invert constructive and practical variations in HHD (HORI, 2016).

The present research is restricted to a couple of researches with limited figures of HHD patients. Only in a single study, long-term anti-hypertensive therapy failing to stabilize LV systolic malfunctions in hypertensive patients with HF and decreased EF. Beta-blockers, incorporating carvadilol, metoprolol, and bisoprolol have enhanced left ventricular ejection fraction (LVEF) and reduced incidence and mortality from HF. Carvedilol lowered the potential risk of demise and hospital care for cardiovascular causes in HF patients obtaining digoxin, diuretics, and renin-angiotensin system inhibitors. In hypertensive clientele, carvedilol also limited cardiovascular incidence, mortality, and HF post-myocardial infarction (MI). Conversely, the impact of carvedilol on LV design and function as well as mortality in patients through HHD is actually not reported. The objective of the research would be to evaluate whether carvedilol is effective in reversing structural and functional changes in the left ventricle and can improve the survival of patients with HHD (James, 2016).

MATERIALS AND METHODS:

This retrospective research was carried out in 2018. The design consisted patients have been managed in a public hospital involving 2015 to 2018.

Criteria of Inclusion and Exclusion

We preferred 1920 patients for such a research. From this total, 1822 were ruled out; 736 were excluded as a consequence of limited data, 1025 had exclusion conditions, and sixty one was without a second control echo-cardiography. The patients have been chosen by convenience trial. Omission criteria incorporated any valvulopathy, non-hypertensive cardiomyopathy, hypothyroidism, hyperthyroidism, infiltrative cardiovascular disease, angina, reported or medical assumed coronary artery disease (CAD), chronic kidney disease (projected glomerular filtration rate <30 mL/1.73 m2/min), additional high blood pressure, cancer, earlier use of chemotherapy, grade III obesity (body mass index (BMI) ⩾40 kg/m2), organ transplantation, diabetes using insulin, or having implantable cardioverter defibrillators.

Collected Variables

Hemodynamic assessment

Heart rate and systolic, diastolic, and mean BP were examined both before and after carvedilol use. Blood pressure and heart rate had been assessed along with the patients in placed position.

Biochemistry and hematologic tests

Complete cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, glucose, creatinine and hemoglobin, and hematocrit were evaluated with commercial kits earlier to and after carvedilol treatment.

Echocardiography

Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), aortic root dimension (AoD), left atrium diameter

(LAD), interventricular septum thickness (IVST), posterior wall thickness (PWT), EF, left ventricular mass index (LVMI), and relative wall thickness (RWT) were evaluated before and after carvedilol use (James, 2016).

Myocardial scintigraphy and coronary angiography

Of 98 study participants, 66 (67%) were evaluated by one or both of these tests. A total of 36 patients had coronary angiography. A total of 30 patients had only myocardial scintigraphy, and 11 patients had both tests.

Statistical Analysis

SPSS version 20 was used for statistical analysis. Normality was tested with Kolmogorov–Smirnov method. Since data for most variables were not normally distributed, findings are reported as median and interquartile range (25th to 75th percentile). Continuous numeric parameters were compared by Wilcoxon test for paired samples; while non-paired variables were compared with Mann–Whitney method. Bivariate analysis with chi-square ($\chi 2$) and Fisher exact test were used for categorical variables. The Kaplan–Meier method and log-rank test were used to estimate survival among HHD with and without improvement of EF during carvadilol treatment. P-values <0.05 were considered statistically significant.

RESULTS:

Study population

A maximum of 98 hypertensive (males and females) patients along with decreased EF (<45%) were considered. Carvadilol was included to their procedures programs, including diuretics and renin-angiotensin system blockers for hypertension and systolic HF. Prior to incorporating carvadilol half of the hypertensive patients had currently accomplished blood pressure control. Subject areas were considered at baseline and 6 years (median) after starting out procedures with carvadilol. CAD was omitted by cinecoronariography, computed tomography (CT) scan, or cardiac scintigraphy. Trial size and drive offers have not been carried out, as this was a convenience preview.

Standard statistic data and other particular detailed data are presented in below mentioned Table 1. All subjects were taking diuretics and renin-angiotensin system blockers and kept medication's dose during treatment, as mentioned in Table 2. Baseline BMI, blood pressure, heart rate, and biochemistry values for all patients are provided in given below Table 3. Seven patients (8%) had side effects; two men reported erectile dysfunction, and five patients reported other side effects such as wheezing, dyspnea or dizziness or symptoms consistent with claudication orhypotension.

Table 1.

Demographic and clinical parameters from all subjects.

Variables	N (%) or median (percentiles 25–75)
Males	59 (60%)
Race	
White	64 (64%)
Black and Mulatto	34 (35%)
Age (years)	55 (47–59)
Diabetes	24 (28%)
Smoking habit	18 (18%)

Source: (James, 2016)

Table 2.

Antihypertensive, antidiabetic, hypolipidemic, antiarrhythmic, digoxin and RAS inhibitors, frequency use, and doses.

Drugs	N (%)	Doses, mg/day, median (percentiles 25–75)
Carvedilol	98 (100)	50 (25–75)
Diuretics	97 (100)	
Spironolactone	43 (44)	25 (25–25)
Thiazide	41 (42)	25 (25–25)
Furosemide	39 (40)	40 (40–80)
RAS inhibitors	97 (100)	
Enalapril	53 (55)	30 (20–40)
Losartan	24 (25)	100 (50–100)
Captopril	19 (19)	75 (25–150)
Valsartan	1 (1)	80
Amlodipin	32 (33)	10 (5–10)
Alfa 2 agonist	11 (11)	0.2 (0.1–0.3)
Digoxin	29 (29)	0.25 (0.25)
Statins	28 (28)	
Simvastatin	17 (61)	20 (15–20)
Atorvastatin	11 (39)	20 (20–20)
Antidiabetic	19 (19)	
Metformin	14 (74)	1700 (850–2125)
Gliclazide	5 (26)	50 (30–60)

Source: (James, 2016)

Table 3.

Baseline biochemical, anthropometric, and hemodynamic variables and comparison after carvedilol use.

Variables	Baseline median, (percentiles 25–75)	After treatment median, (percentiles 25–75)	P value
Glycaemia, mg/dL	100.5 (94.0–117.5)	104.0 (97.0–117.0)	0.036
T-cholesterol, mg/dL	193.0 (172.3–235.0)	183.0 (158.0–220.0)	0.085
HDL-chol, mg/dL	43.0 (33.5–52.0)	45.0 (36.0–56.3)	0.129
LDL-chol, mg/dL	123.0 (98.0–140.0)	111.5 (83.8–137.0)	0.049
Triglycerides, mg/dL	121.0 (85.5–194.0)	115.0 (85.0–176.0)	0.904
Creatinine, mg/dL	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.588
Potassium, mEq/L	4.3 (3.9–4.7)	4.3 (4.0–4.6)	0.418
BMI, kg/m^2	28.8 (25.5–32.6)	29.4 (26.1–32.8)	0.030
Systolic BP, mmHg	140.0 (128.3–160.0)	130.0 (120.0–150.0)	0.004
Diastolic BP, mmHg	90.0 (80.0–100.0)	80.0 (80.0–100.0)	<0.001
Mean BP, mmHg	110.0 (96.4–120.0)	100.0 (90.0–113.3)	<0.001
Heart rate, bpm	80.0 (66.0–94.0)	70.0 (64.0–78.0)	<0.001

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Source: (James, 2016)

In comparison to baseline standards, inclusion of carvadilol at a median dosage of 50 mg per day for a median of 6 years considerably decreased systolic, diastolic, and mean BP along with heart rate (according to details given in Table 3). Body Mass Index and blood glucose enhanced relatively and considerably, while LVESD, LVEDD, and LVMI minimized. LVEF enhanced by an average of 11% after carvadilol treatment (as mentioned in Table 4.

EF enhanced in 69% however did not change or reduced in 31% of patients. We discovered no correlation between median blood pressure and EF before and after treatment ($p = 0.351$, $r = 0.098$). In addition, no correlation is contained between the change in blood pressure and the change in EF between baseline (pre-carvadilol) and carvadilol treatment periods ($p = 0.808$, $r = –0.025$).

Table 4.

Comparison between echocardiographic parameters before and after carvedilol use in all subjects.

Variables	Before treatment median, (percentiles 25–75)	After treatment median, (percentiles 25–75)	P value
LVEF, %	36 (29–44)	47 (36–57)	0.001
LVEDD, mm	62 (56–68)	56 (52–63)	<0.001
LVESD, mm	53 (44–58)	42 (37–51)	<0.001
LVMI, g/m^2	145 (115–200)	129 (103–150)	0.001
LAD, mm	43 (40–49)	42 (39–48)	0.594
IVST, mm	10 (9–12)	10 (9–12)	0.538
LVPW, mm	10 (9–11)	10 (9–11)	0.591
RWT	0.32 (0.28–0.37)	0.36 (0.31–0.40)	0.001

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVCI: left ventricular mass index; LAD: left atrium diameter; IVST: interventricular septum thickness; LVPW: left ventricular posterior wall thicknesses; RWT: relative wall thickness.

Source: (James, 2016)

Standard demographic, hemodynamic, biochemical, and clinical attributes have not been various in between the communities that enhanced rather than those who did not develop LVEF during carvadilol treatment (as provided in Table 5). The group with enhanced LVEF possessed a non-significantly greater carvadilol dose compared to the group lacking betterment in LVEF. Furthermore, the modification in LVEF did not associate with carvadilol dose ($r = -0.158$, $p = 0.246$). Nine patients diminished during follow-up, incorporating 6 patients lacking enhancement in EF and 3 patients with enhancement in EF. Patients that would not have enhanced EF throughout carvadilol had almost six-fold greater mortality (relative risk (RR): 5.7, 95% confidence interval (CI): 1.3–25, $p = 0.022$) during follow-up which ranged from 1 to 10 years (median: 6 years).

Table 5.

Comparison of the demographic, biochemical, anthropometric, and hemodynamic variables, before treatment, in the group that improved versus the one that did not improve the EF.

Variables	EF improvement		P value
	Yes	No	
	n = 68 (69%)	n = 30 (31%)	
Men, n (%)	42 (62)	17 (57)	0.636
DM, n (%)	17 (25)	7 (23)	0.860
Ethnicity White, n (%)	46 (68)	18 (60)	0.466
Tabagism, n (%)	12 (18)	6 (20)	0.775
Age, years	53 (45–59)	56 (50–59)	0.080
BMI, kg/m^2	28 (26–32)	29 (25–33)	0.508
Systolic BP, mmHg	146 (130–160)	140 (120–160)	0.441
Diastolic BP, mmHg	90 (80–100)	90 (80–100)	0.606
Mean BP, mmHg	110 (93–120)	110 (93–120)	0.946
Heart rate, bpm	80 (68–96)	80 (66–90)	0.582
Hemoglobin, mg/dL	15 (13–16)	14 (13–15)	0.758
T-cholesterol, mg/dL	193 (173–221)	206 (171–240)	0.493
HDL-chol, mg/dL	41 (33–49)	47 (41–55)	0.108
LDL-chol, mg/dL	120 (98–140)	128 (97–147)	0.626
Triglycerides, mg/dL	118 (84–192)	115 (85–215)	0.764
Glycaemia, mg/dL	101 (94–118)	100 (97–117)	0.772
Creatinine, mg/dL	1.1 (1–1.3)	1 (0.9–1.2)	0.296

DM: diabetes mellitus; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Source: (James, 2016)

Total mortality following a median six years follow-up of people lacking enhancement of LVEF was considerably higher than subjects with enhancement in LVEF (41% vs. 11%, log-rank and p = 0.009). The estimated 10-year survival was 89% for issues with enhanced EF and only 59% for the group lacking enhanced EF. The classification that improved EF possessed a lower standard EF than the group which did develop throughout carvadilol treatment (as mentioned in Table 6 and Table 7). The group using the most beneficial survival was the one with the highest increase in EF after treatment with carvadilol (EF median = 50.5%), and in the other group the median EF was 38%.

Table 6.

Comparison of medication frequency in the group that improved versus that which did not improv the EF.

Medication	Improve EF median, (percentiles 25–75)	Did not improve EF median, (percentiles 25–75)	P value
Diuretics, n (%)	67 (100)	30 (100)	0.677
Spironolactone	29 (43)	14 (47)	0.758
Thiazide	31 (46)	10 (33)	0.236
Furosemide	26 (39)	14 (47)	0.676
RAS inhibitors, n (%)	68 (100)	29 (97)	0.132
Enalapril	37 (54)	16 (55)	0.863
Losartan	16 (24)	8 (28)	0.770
Captopril	14 (21)	5 (17)	0.629
Valsartan	1 (1)	0	0.236
Amlodipin, n (%)	22 (35	10 (33)	1.000
Alfa 2 agonist, n (%)	9 (10)	2 (2)	0.749
Digoxin, n (%)	21 (31)	12 (40)	0.408
Statins, n (%)	18 (26)	9 (33)	0.338
Simvastatin	9 (50)	2 (22)	0.317
Atorvastatin	9 (50)	7 (78)	0.334
Antidiabetic, n (%)	15 (22)	4 (13)	0.378
Metformin	12 (80)	2 (50)	0.147
Gliclazide	3 (20)	2 (50)	0.236
Time of use carvedilol, month	30 (16–53)	32 (18–44)	0.795
Dose of carvedilol, mg/day	50 (50–50)	50 (25–50)	0.072

Source: (James, 2016)

Table 7.

Comparison of the echocardiographic parameters between the group that improved and the one that did not improve the EF.

Variables	Improve EF median, (percentiles 25–75)	Did not improve EF median, (percentiles 25–75)	P value
LVEF, %	34 (27–42)	45 (34–48)	<0.001
LVESD, mm	53 (45–59)	46 (40–58)	0.162
LVEDD, mm	63 (58–69)	60 (54–67)	0.127
LVMI, g/m^2	153 (125–200)	135 (100–160)	0.065
LAD, mm	44 (40–51)	42 (37–44)	0.052
IVST, mm	11 (9–12)	10 (8–11)	0.051
LVPW, mm	10 (9–11)	10 (8–11)	0.143
RWT	0.32 (0.27–0.38)	0.31 (0.28–0.35)	0.440

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; LVCI: left ventricular mass index; LAD: left atrium diameter; IVST: interventricular septum thickness; LVPW: left ventricular posterior wall thicknesses; RWT: relative wall thickness.

Source: (James, 2016)

Among the 98 patients included in this study, coronary angiography excluded CAD in all of the patients who submitted to this exam, that is, 36 patients (37%). The third (30%) who submitted exclusively to myocardial scintigraphy did not show any evidence of obstructive coronary disease.

DISCUSSION:

In this particular research, ninety-eight consecutive HHD patients taking carvedilol were examined during a mean follow-up of 6 years (1–10 years). The primary outcomes would be the enhancement in EF, cardiac upgrading, and LV mass index. Five- and ten-year endurance in issues taking carvedilol was 98% and 83%, correspondingly. An enhancement in EF was related to better survival at 10 years. Mild raises in blood glucose and Body Mass Index were reported in HHD patients addressed with carvedilol (Dominguez et al., 2019).

The median carvedilol dosage all through the therapy period was 50 mg daily, which is normally much like earlier reports in patients with HF. Unfavorable happenings in connection with carvedilol were caught in 8% of patients and incorporated erectile dysfunction, bronchoconstriction, faintness, lower extremity claudication, and intensifying dyspnea. This volume of negative events was less than that noticed in earlier researches. However, in those studies, issues had a separate etiology for HF, as well as their mean EF was 23% as opposed to 36% in this research. Each of our data raise the possibility that carvedilol is beneficial for hypertensive patients AHA/ACC Stage B HF, that is, structural heart disease but without signs or symptoms of chronic heart HF (Beilin and Mounsey, 2013).

Throughout our study, the EF enhanced starting from a mean of 36% at baseline to 47% on carvedilol. EF enhanced more with carvedilol in patients alongside

reduce baseline standards, that will be equivalent to an earlier study comparing patients with EF <30%. Benefit from antihypertensive drugs as diuretics and renin-angiotensin system blockers on improvement of structure and function of the heart in our sample is possible; however, all subjects were using improved dosages of diuretics and renin-angiotensin system blockers as reported by previous suggestions. Renin-angiotensin system blockers lower blood pressure, reduce LVH, and improve cardiac remodeling (Dominguez et al., 2019)..

Spironolactone is advisable for HF and is related to LV reverse remodeling. Half of the subjects in our study were taking spironolactone, and the dose was optimized before patients started using carvedilol (Dominguez et al., 2019)..

The enhancement of EF in our research is more effective than that noticed in the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction sub-study of HF after MI. Our study excluded subjects with prior MI and/or documented ischemia. Medical records from 1184 patients were analyzed formerly, and 114 (10%) were omitted for earlier MI or CAD identified by cardiac catheterization or scintigraphy. The EF enhanced in approximately 70% of patients.

Sánchez et al. evaluated EF in subjects with HHD and revealed that EF increased in 60% of patients. Conversely, in that research, only 52% of patients were taking beta-blockers, and blood pressure at the beginning of a research was sub-optimally managed (Dominguez et al., 2019)..

During our research, 5 and 10 year endurance levels were 98% and 83%, correspondingly. Ten-year survival was greater among patients with improvement in LVEF than in those without improvement (89% vs 59%). De Carvalho Frimm et al. reported a 73% survival in 90 patients with HHD after 4 years of follow-up. In that study, subjects were not taking beta-blockers. In our study, an association was found between the improvement in LVEF and reduction in mortality. Subjects without an improvement in LVEF had six-fold higher mortality than subjects that had an improvement in LVEF on carvedilol. Choi et al. observed lower mortality among subjects with various etiologies of HF who had LV reverse remodeling with treatment. In the study by Choi et al., only 69.2% of patients were taking beta-blockers, with 91% on carvedilol and 9% on metoprolol. In our study, all patients who had hypertensive cardiomyopathy, were taking diuretics, RAS blockers, and were evaluated after optimization of carvedilol dose. The US carvedilol study showed an association between systolic dysfunction and poor prognosis in HF patients. The US carvedilol trial was one of the first studies to test the safety of carvedilol in 131 patients with HF of different etiologies (Beilin and Mounsey, 2013).

Study limitations include the absence of a control group. However, all patients had some degree of systolic dysfunction on the echocardiogram. As the efficacy of beta-blockers such as metoprolol, bisoprolol, and carvedilol has been demonstrated in patients with systolic dysfunction due to other etiologies, especially ischemic, the ethics of withholding beta-blockers from patients with systolic dysfunction due to HHD are questionable. In our pre-post study design, each patient served as their own control. Potential confounding factors included baseline blood pressure and EF as well as the carvedilol dose during the treatment period. However, baseline blood pressure was similar in the group that improved and the group that did not improve EF on carvedilol as mentioned in Table 5 (Beilin and Mounsey, 2013).

Moreover, no correlations were found between baseline or treatment blood pressure or change of blood pressure between the baseline and carvedilol treatment period and changes in LVEF. The dose of carvedilol was also similar in both groups. Although one criterion for entering the study was optimized treatment of hypertension before carvedilol, some patients has sub-optimal blood pressure since baseline BP averaged 140/90 mmHg. The baseline antihypertensive therapy, which included diuretics and renin-angiotensin system blockers, may have contributed to the improvements in LV structure and function. However, all subjects were using optimized doses of diuretics and renin-angiotensin system blockers at baseline according to previous recommendations. Another limitation of our study is that we could not identify factors, other than differences in baseline EF, which were related to higher survival of the group that had an improvement in EF and better survival. Of note, our study was designed to delineate the mechanisms by which carvadilol improved LVEF and survival in patients with HHD (Björk, Cullhed and Buchholtz, 2017).

CONCLUSION:

As per concluding note, this research indicates that carvedilol, while adding to the treatment of antihypertensive along with the patients with HHD, reversed parameters of remodeling of the left ventricle and increased EF, specifically in patients with baseline EF <34%. Carvedilol also enhances

survival in HHD. The survival considered much better in patients who began the study with stage B HFrEF who had improved LVEF than in patients with stage B HFpEF who did not improve LVEF during carvadilol therapy.

REFERENCES:

1. Beilin, L. and Mounsey, P. (2013). THE LEFT VENTRICULAR IMPULSE IN HYPERTENSIVE HEART DISEASE. *Heart*, 24(4), pp.409-421.
2. Björk, L., Cullhed, I. and Buchholtz, B. (2017). LEFT VENTRICULAR FUNCTION IN ISCHEMIC HEART DISEASE. *Acta Medica Scandinavica*, 190(1-6), pp.223-227.
3. Bollano, E. (2017). Different responses to dobutamine in the presence of carvedilol or metoprolol in patients with chronic heart failure. *Heart*, 89(6), pp.621-624.
4. Dominguez, R., da Costa-Hong, V., Ferretti, L., Fernandes, F., Bortolotto, L., Consolim-Colombo, F., Egan, B. and Lopes, H. (2019). Hypertensive heart disease: Benefit of carvedilol in hemodynamic, left ventricular remodeling, and survival. *SAGE Open Medicine*, 7, p.205031211882358.
5. HORI, M. (2016). Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial1, *1. *American Heart Journal*, 147(2), pp.324-330.
6. James, T. (2016). Outcome of Congestive Heart Failure in Elderly Persons: Influence of Left Ventricular Systolic Function. The Cardiovascular Health Study. Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. *Congestive Heart Failure*, 8(6), pp.346-347.
7. Kahan, T. and Persson, H. (2015). The importance of left ventricular geometry in hypertensive heart disease. *Journal of Hypertension*, 33(4), pp.690-692.
8. Pere, K. (2016). NP009 Failing heart-failing life? The lived experiences of women suffering from chronic congestive heart failure – a meta-synthesis. *Canadian Journal of Cardiology*, 27(5), p.S362.
9. Sun, Y., Hu, S., Wang, L., Hu, Y. and Zhou, J. (2016). COMPARISON OF LOW and HIGH DOSES OF CARVEDILOL ON RESTORATION OF CARDIAC FUNCTION and CALCIUM-HANDLING PROTEINS IN RAT FAILING HEART. *Clinical and Experimental Pharmacology and Physiology*, 32(7), pp.553-560.
10. Yurenev, A., DeQuattro, V. and Devereux, R. (2014). Hypertensive heart disease: Relationship of silent ischemia to coronary artery disease and left ventricular hypertrophy. *American Heart Journal*, 120(4), pp.928-933.