Clinical effect of Perindopril or irbesartan combined with diltiazem moderate primary hypertension outpatients

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Abstract

Objective: To investigate the linical effect of Perindopril or irbesartan combined with diltiazem moderate primary hypertension outpatients.

Methods: A total of 168 mild to moderate hypertension outpatients were randomized to treatment with different anti-hypertensive measures. The subjects were divided into the Diltiazem Group (90mg/d, n=35), RASI Group (150mg/d irbesartan or 10mg/d perindopril, n=45) and CT Group (150mg/d irbesartan + 90mg/d diltiazem or 10mg/d perindopril + 90mg/d diltiazem, n=88). Subjects took examinations of the systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular mass index (LVMI), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), and total ischemia burden (TIB) level before and after treatment during the 6 to 18 months follow-up.

Results: The level of IVST/LVPWT/LVMI in three groups decreased after treatment. SBP, DBP, IVST, LVPWT, and LVMI were decreased significantly after the treatment of RASI ($p<0.05$). Especially, the post-treatment LVMI in the CT group was significantly lower than that of the Diltiazem Group, but the post-treatment results of LVMI in the CT group and RASI group were not statistically different ($P>0.05$). TIB of patients in the CT group and Diltiazem Group decreased at all times before and after treatment, and that the difference in TIB of patients in the RASI Group had no statistical significance ($p>0.05$).

Conclusions: RASI combined with diltiazem can attenuate left ventricular hypertrophy as compared with diltiazem or RASI alone.

Keywords: Perindopril, Diltiazem, Left ventricular hypertrophy, Renin-angiotensin system inhibitor

Introduction

Left ventricular hypertrophy (LVH) is a common target organ damage of hypertension (HT) and is one of the independent risk factors for heart failure, malignant arrhythmia and sudden death [1].

HT patients with LVH have 2 to 4 times of cardiovascular (CV) morbidity and mortality [2], compared with that of hypertensive patients without LVH. LVH in HT is an adaptive response to long-term hypertension, a cardiac compensation closely related to hemodynamic factors, neurohumoral factors, etc [3]. In hemodynamics, blood pressure is considered to be the leading factor of LV remodeling and hypertrophy, and changes in blood pressure level and circadian rhythm are associated with LVH. And in terms of neurohumor, abnormal sympathetic activation, abnormalities in the renin-angiotensin system (RAS) and calcium overload are believed to be important risk factors behind the ventricular hypertrophy in HT. Silent myocardial ischemia (SMI) is often diagnose among HT patients with LVH, due to their relatively low myocardial capillary density, local vascular remodeling and the supply/demand imbalance of myocardial blood oxygen. It is therefore of great importance for HT patients to avert CV events by using antihypertensive agents which have positive effects on LVH and myocardial ischemia. In recent years, studies have shown that RAS inhibitors (RASI) such as captopril and calcium channel blockers (CCB) such as nifedipine controlled-release (CR) tablets can help reduce LVH [4]. By selectively blocking Ca_2^+ channel in smooth muscle cells (SMC) of coronary artery, the Non-dihydropyridine (Non-DHP) CCB diltiazem dilates coronary artery and coronary collateral circulation, promote blood redistribution, relieve myocardial ischemia, reduce the elevated ST segment and thus improve cardiac function.

Currently, animal experiments have confirmed that diltiazem can protect ischemic myocardium and relieve LVH [5, 6]. But it is still under dispute whether RASI can protect ischemic myocardium, despite of its effects of reducing blood pressure and relieving LVH [7, 8]. The combination therapy (CT) of Angiotensin Receptor Blockers (ARB) / Non-DHP CCB have been recommended by many guidelines to treat hypertension. And the results of a large number of clinical trials and basic experiments also confirmed that this combination can dilate blood vessels, reduce inflammatory reactions and enhance the vascular endothelial function by raising the concentration of nitric oxide (NO) in the blood vessels and reducing the concentration of

Interleukin-4 (IL-4) and C-Reactive Protein (CRP), etc. In a recent prospective clinical study, our team divided HT patients into three groups, respectively treated by irbesartan, diltiazem, and irbesartan/diltiazem combination. We followed those patients for the next three years and found that patients treated with CT shown significantly higher level of flow-mediated dilatation (FMD), which was even close to that of the control group. It is thus suggested that the irbesartan/diltiazem CT can improve the vascular endothelial function. The drug therapy combining Irbesartan or perindopril with diltiazem is one of the anti-hypertensive combination therapies using ACEI/ARB+CCB, as recommended in the clinical treatment guideline.

Through the follow-up visits to 168 patients with primary hypertension, this study examines the effect of RASI/diltiazem combination therapy on LVH and myocardial ischemia in hypertension patients, thus providing a theoretical basis for using combination therapies for HT patients in clinical treatment.

Objects and Methods

Objects

We selected untreated patients with mild and mild primary HT who were admitted to the Clinic or being in-patients in the No.2 hospital of Dalian Medical University from January 2015 to April 2018. Inclusion criteria: (1) patients who meet the diagnostic criteria for hypertension according to the *Guidelines for Hypertension Prevention and Control (2005 Edition)* [9]: three blood pressure measurements (BPM) all satisfy that the systolic pressure should be no less than 140 mmHg and/or diastolic pressure ≥ 90mmHg (1mmHg = 0.133kPa); (2) patients who have complete medical records and receive regular reexamination 6 to 8 months after the treatment; (3) the patients' Left Ventricular Mass Index (LVMI) should be no less than 125 g/m2 (for male) or 110g/m2 (for female).

Exclusion criteria: (1) patients with second- and third-degrees atrioventricular (AV) block, sick sinus syndrome (SSS), atrial fibrillation, complete bundle branch block, Wolff-Parkinson-White

syndrome (WPW); (2) patients with chronic wasting diseases (CWD) or malignant tumors; (3) patients with thyroid, liver, kidney or pancreatic diseases; (4) patients whose alanine aminotransferase (ALT) > 150U/L or whose creatinine > 350μmol/L; (5) patients with hypertrophic cardiomyopathy or type 2 diabetes mellitus; (6) patients who had a cerebral stroke within 6 months prior to the treatment; (7) patients with congestive heart failure; (8) women who were pregnant or likely to become pregnant; (9) those who are allergic to drugs used in the subject or had myocardial infarction, stroke or severe arrhythmia during follow-up visits; and (10) patients whose medical records were incomplete. All subjects were screened in accordance with clinical trial requirements of the ethics committee and signed informed consent forms.

Methods

This study, as a prospective one, included altogether 168 subjects in compliance with the abovementioned criteria. According to different anti-hypertensive measures, the subjects were divided into the Diltiazem Group (90 mg/d, n=35), RASI Group (150 mg/d irbesartan or 10 mg/d perindopril, n=45) and RASI/Diltiazem Group (150 mg/d irbesartan + 90 mg/d diltiazem or 10 mg/d perindopril + 90 mg/d diltiazem, n=88). After two weeks, if the blood pressure is higher than 160/100 mmHg, the subjects will be given more antihypertensive drugs (diuretics preferred, and beta-receptor blockers to those with poor heart rate). Detailed records were taken down, including subjects' name, sex, age, height, body mass, smoking history (over 5 cigarettes per day for over 5 consecutive years), drinking history (at least 50 g liquor per day for over 5 consecutive years), family history of hypertension and past medical history (PMH) of chronic diseases. Before entering the group, subjects took BP measurement by the same person (to take the average of the results on 3 different days), took tests of blood, liver and kidney function, blood lipids and fibrinogen (which would be reexamined after treatment), and got examinations of echocardiography and dynamic electrocardiography (DCG). The 168 patients with primary hypertension received follow-up visits after treatment for 6 to 18 months—some more than 18 months—with an average of 13.91 months. In follow-up visits, subjects took examinations of

echocardiography and DCG, the results of which were taken as data for efficacy analysis in different stages.

Measuring Biochemical Indicators

All subjects discontinued using all vasoactive drugs for three days and had a light diet. Three days later and with 12 hours on an empty stomach, subjects would be drawn venous blood to conduct blood test, as well as tests on blood lipids, liver and kidney function and fibrinogen. All specimens were measured by the same fully automatic chemistry analyzer HITACH 7170A under the standardization conditions of the biochemical laboratory of our university.

BP measurement

Subjects were not allowed to smoke or drink tea or coffee 30 min before BP measurement, and should have done a 15-minute wall sit. BP was measured at right brachial artery with a corrected mercury sphygmomanometer. We read systolic pressure at the Phase 1 of Korotkoff sounds and diastolic pressure at Phase 5 of Korotkoff sounds, and took the average of three measurements at the interval of 1 to 2 min.

Echocardiography

All subjects took examinations with Color Doppler echocardiography. In line with the measurement method recommended by the American Institute of Ultrasound in Medicine (AIUM), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular end diastolic diameter (LVEDd) were measured before and after treatment for 3 to 5 consecutive cardiac cycles. The left ventricular mass (LVM), and left ventricular mass index (LVMI) were calculated according to the Devereux correction formula.

DCG

All subjects were tested for MV1, MV5, aVF (lead V) for 24 hours via three-track tape recorders (USA Grand Pacific) and DCG heart rate variability analyzer (TECT8000) [10]. Professionals marked the ST segment changes in DCG and screened out the pseudo-difference waves. Three "one" standards should be met to diagnose myocardial ischemia via DCG: with the equipotential line being the baseline, 1 mm ST depression (either horizontal or down sloping) for over 1 minute at intervals of more than 1 minute. If the ST depression had already occurred, another 1mm depression (horizontal or down-sloping) would be expected on this basis.

Measurement of Total Ischemia Burden (TIB)

TIB refers to the product of the range and time of ST depression in a specific period of time. According to Shi Yajun et al., TIB is the sum of the range and time of ST depressions aroused by myocardial ischemia and shown in MV1, MV5 and aVF leads over the last 24 hours.

Statistical analysis

Continuous variables were averaged, expressed as mean±SD, and compared using the LSD-t test among different groups and using the t-test to compare variables within the group before and after treatment. x^2 test was used to compare the discontinuous variables. All statistical analyses were performed using the SPSS 19.0 package for windows. The null hypothesis was always rejected for $p<0.05$.

Results

Baseline Information

The authors collected a total of 168 cases of primary HT patients (95 men and 73 women) with an average age of (66.0±9.5). The pre-treatment differences in age, gender, drug history and HT course are of little statistical significance; the difference in triacylglycerol and lipoprotein B1 between Diltiazem Group and RASI Group, however, was of statistical significance (see Table 1)

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Table 1 Baseline characteristics of 168 cases of primary HT patients

	CT (n=88)	Diltiazem (n=35)	RASI (n=45)
Age (years)	67.0±10.4	65.41±7.11	64.02±10.81
Gender(male/female)	51/37	19/16	25/20
BMI(kg/m^2)	28.45±4.82	28.37±5.02	28.15±4.77
LDL-c(mmol/L)	123.42±23.42	124.11±21.58	122.73±27.04
eGFR($ml/min/1,73m^2$)	90.83±32.33	91.12±33.27	90.89±34.21
Course of hypertension (years)	11.4±6.1	10.31±5.92	9.42±5.72
TBil (μmol/L)	12.49±2.73	14.29±3.11	13.59±3.05
HDL-C(mmol/L)	1.18±0.31	1.36±0.45	1.34±0.38
ApoA1(mmol/L)	1.31±0.28	1.32±0.24	1.34±0.21
ApoB1(mmol/L)	0.98±0.24	0.88±0.22	1.05±0.17
FIB(mmol/L)	3.64±0.39	3.42±0.45	3.35±0.68
ALT(U/L)	25.51±10.72	25.29±12.11	25.19±10.87
AST(U/L)	25.19±5.73	26.21±7.74	24.99±6.23
LDH(U/L)	164.59±21.22	170.86±47.44	171.46±34.28
UA(μmol/L)	363.96±97.79	382.91±84.56	363.33±74.37
SCr(μmol/L)	82.53±23.49	71.12±14.52	73.65±15.23
TC(mmol/L)	4.67±1.12	4.66±1.12	4.86±0.72
TG(mmol/L)	1.64±0.82*	1.40±0.54	1.85±0.81*

Note: *TBil* Total bilirubin, *LDL-c* High-density lipoproteins cholesterol, *HDL-C* High-density lipoproteins cholesterol, *ApoA1* Apolipoprotein A1, *ApoB1* Apolipoprotein B1, *FIB* Fibrinogen, *ALT* Alanine aminotransferase, *AST* Aspartate Transaminase, *LDH* low-density lipoprotein, *UA* Uric acid, *SCr* serum creatinine, *TC* Total Cholesterol, *TG* triacylglycerol, *eGFR* estimated glomerular filtration rate, *the value has statistical significance compared with Diltiazem group ($p<0.05$).

Effects of RASI/Diltiazem Combined Treatment (CT) on Blood Pressure

Results show that the systolic pressure that treated with single kind of drug within two groups had no statistical difference, while that of the CT group was statistically higher than that of the other two. Besides, the diastolic pressure between the three groups has shown no statistical difference. Both systolic pressure and diastolic pressure witnessed a decrease in the three groups after the treatment, in which the CT group outperformed the other two groups in terms of the reduction of systolic pressure (see Table 2).

Table 2 Influence on hypertension of different groups (mean±SD, mmHg)

Pressure		CT (n=88)	Diltiazem (n=35)	RASI (n=45)
Systolic pressure	Pre-treatment	167.50±6.59	156.58±8.77[a]	154.11±10.68[a]
	Post-treatment	129.41±3.72[b]	127.01±6.28[b]	125.78±7.41[b]
	Difference	38.09±5.10	29.60±4.17[a]	28.32±5.20[a]
Diastolic pressure	Pre-treatment	97.01±8.81	95.38±2.49	93.41±8.90
	Post-treatment	73.49±6.51[b]	76.58±8.18[b]	75.11±5.61[b]
	Difference	23.40±6.21	18.80±5.11	18.18±4.09

Note: a $p<0.05$ when compared with CT group; b $p<0.05$ when compared before treatment within the same group.

Effects of RASI/Diltiazem CT on Ventricular Structure

The pre-treatment level of IVST/LVPWT/LVMI in the three groups of patients had no statistical difference. The level of IVST/LVPWT/LVMI in three groups decreased after treatment. Especially, the post-treatment LVMI in the CT group was significantly lower than that of the Diltiazem Group, but the post-treatment results of LVMI in the CT group and RASI group were not statistically different (see Table 3).

Table 3 The influence on ventricular structure of different groups (mean±SD)

Ventricular structure		CT (n=88)	Diltiazem (n=35)	RASI (n=45)
IVST(mm)	Pre-treatment	1.25±0.11	1.23±0.09	1.23±0.11
	Post-treatment	1.03±0.09[a]	1.09±0.07[a]	1.07±0.06[a]
LVPWT(mm)	Pre-treatment	1.14±0.07	1.13±0.05	1.14±0.10
	Post-treatment	1.00±0.07[a]	1.06±0.08[a]	1.03±0.09[a]
LVMI(g/x^2)	Pre-treatment	126.87±15.67	125.99±18.27	126.45±19.31
	Post-treatment	104.53±13.50[a]	112.80±16.16[ab]	108.11±15.12[a]

Note: a $p<0.05$ when compared before treatment within the same group. b $p<0.05$ when compared with CT group.

Effects of RASI/Diltiazem CT on TIB

After treatment, decrease was shown in the TIB of MV5 and aVF leads and overall TIB both in CT group and Diltiazem Group, while the TIB difference of MV1 lead were of no statistical significance. RASI Group showed no statistical differences in TIB on all three leads and the overall TIB. The level of overall TIB of the CT group and Diltiazem Group dropped more sharply than that of the RASI Group (see Table 4).

Table 4 Influence on TIB of different groups [mm/(min.24h)]

ECG leads		CT (n=88)	Diltiazem (n=35)	RASI (n=45)
MV5	Pre-treatment	1.78±0.69	1.18±0.54	0.92±0.47
	Post-treatment	0.96±0.47[a]	0.62±0.38[a]	0.83±0.36
MV1	Pre-treatment	1.52±0.60	1.35±0.57	0.79±0.36
	Post-treatment	1.13±0.44	0.91±0.36	0.68±0.28
aVF	Pre-treatment	1.42±0.51	1.48±0.63	0.66±0.28
	Post-treatment	0.80±0.34[a]	0.82±0.30[a]	0.60±0.26
Total TIB	Pre-treatment	2.26±0.92	1.97±0.76	1.12±0.47

	Post-treatment	1.42±0.59[a]	1.25±0.57[a]	1.07±0.45
% of total TIB decreased (%)		37.17[b]	36.54[b]	4.46

Note: a $p<0.05$ when compared within the same group before treatment, b $p<0.05$ when compared with the RASI group.

Effects of RASI/Diltiazem CT on TIB at Different Time Periods

The follow-up visits involved each and every patient at every point in time with no one missed, so the data for each patient at any given time is complete. The result turned out that TIB of patients in the CT group and Diltiazem Group decreased at all times before and after treatment, and that the difference in TIB of patients in the RASI Group had no statistical significance (see Table 5).

Table 5 Influence on TIB at different time of each group (mean±SD) [mm/(min.24h)]

Group		TIB			
		0~6 months	6~12 months	12~18 months	18~24 months
CT (n=88)	Pre-treatment	1.77±0.74	1.68±0.69	1.79±0.67	1.73±0.67
	Post-treatment	0.94±0.41[a]	0.99±0.46[a]	1.00±0.38[a]	0.92±0.35[a]
Diltiazem (n=35)	Pre-treatment	1.41±0.58	1.28±0.54	1.64±0.61	1.17±0.46
	Post-treatment	0.78±0.35[a]	0.76±0.38[a]	0.92±0.38[a]	0.64±0.27[a]
RASI (n=45)	Pre-treatment	0.84±0.38	0.83±0.37	0.81±0.35	0.94±0.41
	Post-treatment	0.74±0.41	0.75±0.34	0.70±0.31	0.85±0.35

Note: a $p<0.05$ when compared within the same group before treatment.

Discussion

This study, through follow-up visits and observation to 168 primary HT patients who adopted different antihypertensive drugs, found that irbesartan or perindopril and diltiazem had the effect of lowering blood pressure and relieving LVH; diltiazem can relieve myocardial ischemia, yet

irbesartan and perindopril have little effect in this regard. RAS plays a vital role in the course of primary HT, and in recent years clinicians have been using RAS control as an important means to reduce blood pressure. As a non-DHP calcium antagonist, diltiazem can lower blood pressure by relaxing the peripheral vascular smooth muscle. However, the extent to which it lowers blood pressure is related to how much blood pressure has been raised, so it only shows a mild antihypertensive effect to normotensives. Besides, diltiazem does not affect the the blood supply for heart, brain, kidney and other important organs while controlling blood pressure. Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) found that, compared with the traditional antihypertensive treatment (atenolol + bendroflumethiazide), ACEI + CCB (amlodipine + perindopril) offered better cardiovascular protection [11]. Although this study carries out prospective case analysis, the subjects were not randomly grouped; but rather, they were given reasonable choice of antihypertensive drugs according to their specific levels of blood pressure [12]. The differentiated baseline of systolic pressure of patients in three groups explains the real clinical situations. In this study, before and after treatment, the level of IVST, LVPWT and LVMI in each group of patients had no statistical difference, which ensured the comparability of each group. It is found that combined treatment was more effective in lowering systolic pressure than single drug therapies, yet the difference in diastolic pressure was of no statistical significance.

LVH, an important complication of hypertension, can indirectly lead to myocardial ischemia, and eventually heart failure and arrhythmia [13]. The prevention and reverse of LVH, therefore, is an important goal of HT treatment, as well as an important evaluation method on the efficacy of antihypertension drugs. Hypertension may increase the activity of sympathetic nerve and the synthesis and secretion of norepinephrine; it may also activate beta-adrenoceptor and accelerates the production of glycogen and cyclic adenosine monophosphate and the synthesis of total protein content and noncontractile protein in cardiomyocyte, thus eventually resulting in ventricular hypertrophy [14, 15]. Closely related to the formation of LVH, vasoactive substances such as norepinephrine (NE) and angiotensin II (Ang II) directly stimulate cell growth and regulate the

cell's adaptive response to the pressure load as the secondary signaling molecules. Acting on α and β receptors, NE can lead to the occurrence and exacerbation of hypertension and is an important risk factor of ventricular remodeling and myocardial ischemia [9, 16]. In our earlier study, it was found that captopril could decrease the NE level in cardiomyocytes of HT rats and have antisympathetic effect and the effect of reversing LVH [17]. The circulatory system and cardiac RAS are involved in the process of myocardial hypertrophy. Among all neuroendocrine factors, Ang II is the leading factor of LVH. Angiotensin converting enzyme inhibitor (ACEI) and ARB can block Ang II by intervening the regulatory mechanism of neuroendocrine and also delay the progression of coronary atherosclerosis by affecting fibrinolytic balance, vascular endothelial function, inflammatory processes and the stability of platelets, thus preventing myocardium from ischemia. ACEI is currently considered to be the most effective drug to reverse LVH [5, 18]. Though blocking the binding of Ang II and AT_1 receptor with high selectivity and efficiency, ARB can inhibit the Ang II-mediated vascular constriction, sodium and water retention, increased sympathetic nerve activity, cell hyperplasia and many other physiological effects associated with hypertension. So, it has the effect of protecting the heart and vessels and reversing LVH, in addition to blood pressure control. Apart from RASI, numerous studies have shown that CBB can also effectively relieve LVH of HT patients. In the study on the effect of nifedipine and enalapril on reversing LVH, it was found that CBB brought about similar effects when blood pressure dropped at the same rate but should be taken for more than 6 months to effectively relieve LVH, according to a number of scholars [1, 3, 18]. It is also confirmed that combined treatment can protect the target organs more effectively. This study found that patients in the single and combined drug groups had significantly reduced IVST, LVPWT, and LVMI after treatment. Compared with RASI such as perindopril or irbesartan, diltiazem excels in relieving left ventricular ischemia, while RASI in reversing LVH.

40% to 50% of HT patients have the complication of myocardial ischemia, of which 75% is shown as silent myocardial ischemia (SMI) [2]. The underlying reason of SMI in HT is: (1) hypertension

is a risk factor for atherosclerosis and can trigger organic stenosis and dynamic stenosis (spasms) of coronary artery; (2) even without atherosclerotic stenosis in coronary artery, HT patients may also have different degrees of reduction in coronary artery blood flow; (3) HT patients are likely to have activity in sympathetic nerve, the increased heart rate aroused by which may induce myocardial ischemia; (4) for HT patients with LVH, the relatively low density of myocardial capillaries and remodeled vascular wall may affect the supply-demand balance of myocardial blood oxygen, which explains why clinical manifestations such as angina, myocardial ischemia and arrhythmia can also occur in HT patients without atherosclerotic stenosis in coronary artery. DCG monitors the EC changes in 24 hours and thus helps better detect SMI. It is found that SMI is more likely to occur between 6:00 and 12:00, and less between 0:00 and 6:00. In clinical work, TIB, being the major quantitative evaluation factor of myocardial ischemia, can comprehensively reflect the degree of myocardial ischemia and clinical prognosis. Diltiazem, as a non-DHP CBB, has satisfying anti-myocardial ischemia effect, the mechanism of which includes: (1) by inhibiting the influx of calcium ions in coronary artery and SMCs of surrounding vessels and easing calcium overload in myocardial cells, it can not only dilate coronary artery and relieve coronary artery spasms, but also dilate the peripheral small arteries and mitigate the body circulation resistance and cardiac afterload; (2) diltiazem can directly and forcefully dilate the coronary artery to reduce vascular resistance in the narrowed parts of coronary artery; (3) it increases the blood flow in the coronary artery and improves the perfusion of remote ischemic myocardium by boosting the collateral circulation; (4) it prevents the structure and function of mitochondria from damaged, thereby preventing myocardial ischemia.

Conclusion

In this study, it is found that the overall TIB (24h) of patients both in Diltiazem Group and the CT Group decreased significantly after treatment, yet the difference between the two groups was of little statistical significance, indicating the anti-myocardial ischemia effect of diltiazem. Though without the effect of directly dilating coronary artery and the inotropic and chronotropic effects, ACEI is proved, in the studies of Tang Linqing and Wang Xining et al., to have anti-myocardial

ischemia effect. This study found no statistical difference of TIB in patients using irbesartan or perindopril in different time slots before and after the treatment; its downward trend may be due to the limited size of samples. This study is based entirely on real clinical situations, so there is a mismatch between the dose of the single drug groups and the CT group. And there is no statistical difference in the pre-treatment ventricular structure of the 3 groups of patients, as well as the ratio of statins, β-receptor blockers, diuretics, aspirin and clopidogrel used in the course of treatment. But it should be admitted that a certain degree of selective bias may exist, including bias against patients and detecting signal and prevalence-incidence bias, and that there exists a certain degree of data mismatch, such as regional differences, different gender, psychology, emotions, exercise habits, etc., which are to be avoided in the following studies.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Second Hospital of Dalian Medical University.

Human and animal rights

The study was conducted in accordance with the Declaration of Helsinki principles. Biomedical research with humans as subjects must require the informed and consent of the subjects, and human health must be maintained.

Consent for Publication

Not applicable.

Availability of data and materials

The dataset that support the results and findings of this research are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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