Long-Term Association between Intensive Medical Treatment and the Incidence of Cardiovascular Outcomes in Patients with Dyslipidemia: an Observational Study

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ABSTRACT

Introduction: The management of patients with dyslipidemia (DLP) requires intensive medical follow-up as an essential part of treatment and to reduce the risk of cardiovascular (CV) outcomes. The aim of this study was to evaluate whether adherence to medical treatment changed the prevalence of CV disease events in a retrospective 7-year follow-up analysis.

Methods: This retrospective study involved 92 patients divided into two groups according to their adherence: the REG group with 64 patients who had medical appointments from 2012 to 2018, and the DROP group, with 28 patients who had medical appointments in 2012 but did not complete regular appointments until 2018. Cox proportional hazard models were fitted to estimate hazard ratios associated with CV outcomes as primary endpoints.

Results: We observed a total of 32 cases of acute myocardial infarction (AMI) in the study population, 17 (338.41 pY) in the REG group and 15 (62.97 pY) in the DROP group. An increased hazard of AMIs was observed in the DROP group compared with the REG group by follow-up time ($p < 0.001$). We found that previous events of AMI and congestive heart failure (CHF) were associated with progression to treatment dropout ($p < 0.05$) and that two drugs were considered a risk factor for treatment dropout, diuretics and fibrates ($p < 0.05$).

Conclusions: A reduced hazard of AMI was observed in patients who complete a greater number of medical appointments and receive multidisciplinary treatment on a regular basis.

Keywords: Dyslipidemia; Multidisciplinary care team; Cardiovascular disease; Myocardial infarction

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Key Summary Points

(1) Regular medical and multidisciplinary treatment is associated with reduced hazard of AMI.

(2) There is an improvement in HDL cholesterol (HDL-c) levels in patients on regular medical treatment compared with dropout patients.

(3) Use of medications such as diuretics and fibrates increase the risk for treatment dropout.

(4) Patients with the presence of previous events of both AMI and CHF had a greater chance of not adhering to follow-up clinic management.

(5) Greater adherence to multidisciplinary treatment with a nutritionist is probably the key finding associated with reduced hazard in CV outcomes.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide. According to data from the National Health and Nutrition Examination Survey (NHANES) 2015–2018, the prevalence of CVD was 49.2% overall in adults $\geq$ 20 years of age (126.9 million in 2018), and increased with age in both men and women [1, 2].

Several risk factors contribute to the etiology and development of CVD, especially dyslipidemia (DLP) and type 2 diabetes mellitus (T2DM). Although contemporary data show a significant decrease in CVD rates in individuals with DLP and T2DM, both diseases remain highly prevalent and are important risk factors for CVD [3, 4]. There is still little evidence whether a regular and more comprehensive multidisciplinary approach in the treatment of CV risk factors in adults with DLP and T2DM can reduce CV events. The intensive treatment

of DLP in adults with T2DM is discussed in the relevant sections of the latest evidence-based guidelines of the Brazilian Society of Cardiology, the European Society of Cardiology, and the American Heart Association [1–4].

Although there is robust evidence regarding the long-term efficacy of clinical treatment for controlling individual risk factors in patients with DLP and T2DM [3, 4], little is known about the effect of intensive multidisciplinary or multifactorial strategies that affect the various risk factors of patients with established CVD [5–7]. Overall, they found that high-risk CV patients with long-standing DLP and T2DM had a 50% reduction in the risk of CV events and mortality when they receive intensive multidisciplinary treatment [5]. In another study, after 5 years of multidisciplinary treatment, the rate of CV events (including mortality, CV morbidity, and revascularization) is 17% lower in patients undergoing intensive treatment than in those undergoing usual treatment [6]. According to the Steno2 study in Denmark, which compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for CV disease in patients with T2DM, there is a reduction of 50% in CV and microvascular events [7].

Evaluating the long-term effects of a multidisciplinary intervention, including medical and nutritionist consultations, can assist in the development of guidelines, education, and training regarding CV outcomes for primary care teams [5–8]. Chronic diseases related to nutrition, such as CVD and T2DM, represent an increasingly significant health burden for the population [8, 9]. Given the ability of dietary modification to improve the biomarkers of chronic diseases, the participation of nutritionists in promoting behavior changes is recognized as a first-line approach for CV diseases [9].

Intensive follow-up with regular medical and nutritional consultations is essential to ensure that patients correctly adhere to drug treatments and achieve their therapeutic goals [10]. Among almost all cute myocardial infarction (AMI) patients, approximately half discontinue medications 12 months after the AMI. Greater

interaction among medical teams and patients enables better adherence to medical treatment by 55%; however, it is not associated with greater adherence to medications [11].

Thus, the aim of the study was to evaluate how adherence to multidisciplinary treatment and a greater number of medical consultations affected CV outcomes in patients with DLP and T2DM who were followed up for 7 years. We also evaluated the effect of medical follow-up on the lipid profile, hospitalizations, and the number of medications used, and assessed the prevalence of T2DM.

METHODS

Ethical Aspects

The present research project was developed according to the recommendations of resolution no. 466/2012 and the Declaration of Helsinki, modified in Hong Kong in 1989, for research involving humans. The research project was submitted to and approved by the Research Ethics Committee of the National Institute of Cardiology (NIC) and was registered with the National Research Ethics System on 9 June 2020 (31565920.3.0000.5272). The informed consent form was sent by mail and digitally, and consent was given digitally and through an audio recording owing to the COVID-19 pandemic. The researchers maintained the confidentiality and integrity of the information.

Study Design and Population

This was a retrospective study involving patients treated at the lipids and T2DM service of the NIC from 1 January 2012 to 31 December 2018. Convenience sampling of all patients with DLP who were treated at the outpatient clinic of the NIC in 2012 was used. Ninety-two patients were divided into two groups: The REG group, which comprised 64 patients who maintained medical appointments from 2012 to 2018 (with the last consultation performed between 1 January and 31 December 2018), and

the DROP group, which comprised 28 patients who underwent medical consultations in 2012 but did not continue regular consultations until 2018.

To be included, patients were required to have the following two characteristics: (1) Being an adult of either sex aged between 35 and 75 years and (2) having attended the DLP and T2DM services of the NIC in 2012. Cancer patients, wheelchair users, pregnant women, lactating women, and patients with active tuberculosis, mental alienation, multiple sclerosis, leprosy, Parkinson's disease, ankylosing spondylarthrosis, severe nephropathy, advanced stages of Paget's disease, and acquired immunodeficiency syndrome were excluded.

The participants' clinical variables were recorded on a specific form and included their name, age, sex, history of smoking, physical exercise, systemic arterial hypertension (SAH), T2DM, angina, previous diseases, CV events, AMI, cerebrovascular accident (CVA), CVD, and number of outpatient medical visits during the study period. All medical records of patients treated at the outpatient clinic of the DLP and T2DM services were evaluated throughout 2012. To evaluate possible deaths, changes in address indicating a move to another city, and follow-up treatment at other hospitals, the patients were contacted by telephone, and the information that was acquired was added to a form developed specifically for the study.

Adherence was assessed according to the number of consultations completed during the 7-year study period, and patients were deemed adherent to multidisciplinary treatment if they had completed at least two annual visits to the outpatient clinic and at least one consultation with the nutritionist during the 7-year study period. Adherence to drug treatment could not be evaluated in this study; however, it was possible to determine the profile of the drugs that the patients used during the study period.

The anthropometric variables analyzed were weight, height, body mass index, waist circumference, and blood pressure. Patients' laboratory test results were assessed at two time points: 2012 and 2018. Our analysis included the following tests: total cholesterol (CT), low-density lipoprotein cholesterol (LDL-c), high-

density lipoprotein cholesterol (HDL-c), triglycerides, fasting glycemia, glycated hemoglobin (HbA1c), creatine phosphokinase (CPK), and C-reactive protein (CRP).
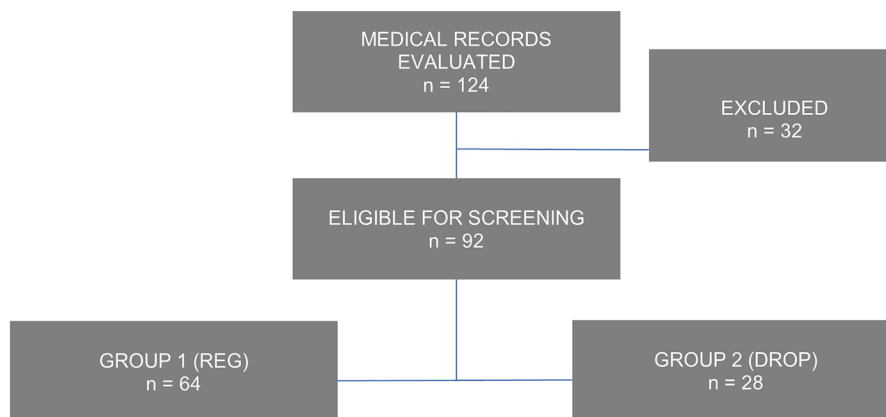
Statistical Analysis

The collected data were tabulated in a spreadsheet using the double-entry technique for validation. In the evaluation of the differences in sociodemographic, clinical, and laboratory characteristics between the two groups, for continuous numerical variables, the Mann–Whitney U test was used to evaluate the hypothesis that the different samples were taken from the same distribution or from distributions with the same median. Similarly, for categorical nominal variables, chi-square tests were used to evaluate the differences in frequencies between the different groups to verify the hypothesis of independence between the groups and these variables. For inferences, multiples statistical models were applied. For the analyses of the use of medications and the experience of CV events by patients between groups, binomial (logit link function) generalized linear models were fitted. For the analysis of progression to a CV event by patients between groups, a time-to-event analysis, Cox proportional hazard models were fitted. For the analysis of the number of medications used by patients between groups, negative-binomial (logarithmic link functions) generalized linear models were fitted. Finally, for the analysis of patients' main groups of lipids between groups, linear models were fitted. Regardless of the fitted model, to eliminate the sample bias, confounding variables were selected using bivariate models and were included in the multivariate models if their adjusted p-value was < 0.2. All models included age, sex, schooling years, established T2DM, and marital and working status as confounding factors. Binomial models for the experience of CV events, Cox proportional hazard models for the analysis of progression (time-to-event) to a CV event, negative-binomial generalized linear models for the analysis of the number of medications used, and linear models for the analysis of main groups of lipids, also included body mass index (BMI) and auto-declared skin color as confounding factors. Odds-ratio (OR), relative-risk (RR), and hazard ratio (HR) were used to represent relative risks in binomial, negative-binomial, and Cox proportional hazard models, respectively. All statistical analyses were performed in R v. 3.6.1. Results with two-tailed p-values < 0.05 were considered significant.

RESULTS

A total of 124 medical records of patients treated at the lipid and T2DM outpatient clinic during 2012 were evaluated. A total of 32 patients were excluded, including three patients who were under 35 years of age and 28 patients with chronic disabling diseases who were older than 76 years of age (Fig. 1). The study population had a mean age of approximately 67 years, and most were men (54.3%), elderly (58.7%), white (58.7%), and married (63.3%). The REG group consisted of 64 patients who were followed up until 2018, and the DROP group comprised 28 patients who did not adhere to treatment until 2018 (Table 1). We observed a median follow-up time of 5.72 (IQR = 1.37) years of the study population, including 5.97 (IQR = 0.60) years in the REG group and 3.63 (IQR = 2.21) years in the DROP group. We observed that the patients who were most active in the labor market were the least adherent to regular treatment; these patients comprised 71.4% of the DROP group and 45.3% of the REG group (p = 0.002). Regarding education, 30.7% of the participants had at least 10 years of education. Regarding anthropometric parameters, patients with a body mass index (BMI) of 28.25 kg/m^2 (overweight range of 25.0–29.9 kg/m^2) were considered overweight according to the World Health Organization classification. The median systolic [a]blood pressure of the study population was 136 mmHg, the diastolic blood pressure was 80 mmHg, and 93.5% of the individuals had a diagnosis of SAH. We observed a prevalence rate of 75% for T2DM. A total of 46.7% of the studied patients had current or previous angina, indicating that the study population had a high degree of CV risk.

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                    │   MEDICAL RECORDS       │
                    │     EVALUATED           │
                    │      n = 124            │
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                                │                        │   EXCLUDED       │
                                ├────────────────────────│    n = 32        │
                                │                        └──────────────────┘
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                    │ ELIGIBLE FOR SCREENING  │
                    │        n = 92           │
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  │   GROUP 1 (REG)      │              │   GROUP 2 (DROP)     │
  │      n = 64          │              │      n = 28          │
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Fig. 1 Recruitment flowchart for the study

Regarding lifestyle, the prevalence of a sedentary lifestyle was 83.7%, and the prevalence of smoking was 30.4%. Regarding the number of nutrition consultations according to the follow-up time, a total of 57 consultations were observed in the study population, 76.6% of the REG group had at least one nutrition consultation versus 28.6% of the DROP group.

We found no association of previous diseases, namely myocardial revascularization surgery (MCRS), percutaneous transluminal coronary angioplasty (PTCA), or dilated cardiomyopathy (DCM), with adherence to follow-up clinical management, but an association with AMI and congestive heart failure (CHF) was identified (Table 2). Patients with previous events of both acute AMI [aOR = 33.63 (2.09–541.42), $p = 0.026$] and CHF [aOR = 103.64 (2.38–4511.47), $p = 0.031$] had a greater chance of not adhering to follow-up clinic management than those who had not experienced these events previously.

We evaluated the risk factor associated with treatment dropout based on medication use measured at baseline (Table 3). We observed that two drugs were considered a risk factor for treatment dropout, diuretics [aOR = 43.33 (2.23–841.39), $p = 0.025$] and fibrates [aOR = 320.01 (3.97–25809.74), $p = 0.020$]. Despite statins being the most used drug, we did not observe any association of risk or protection for treatment dropout [aOR = 0.16 (0.01–2.58), $p = 0.396$]. The same was observed for widely used drugs such as beta blockers [aOR = 8 (0.05–1269.03), $p = 0.842$], antiplatelet agents [aOR = 3.22 (0.47–21.98), $p = 0.464$], and metformin [aOR = 2.86 (0.18–46.43), $p = 0.921$].

In the evaluation of the number of CV events along the study period, when we compared the two groups, we observed a total of 32 cases of AMI in the study population: 17 (338.41 pY) in the REG group and 15 (62.97 pY) in the DROP group. In fact, AMI was strongly associated with progression to treatment dropout [aHR = 15.282 (3.26–71.645), $p < 0.001$]. We observed a total of 53 hospital admissions during the study period: 29 (295.74 pY) in the REG group and 24 (51.58 pY) in the DROP group. However, the number of hospital admissions was not associated with progression to treatment dropout [aHR = 14.561 (4.496–47.157), $p = 7.927$]. A total of five cases of stroke were observed: three (379.56 pY) in the REG group and two (90.24 pY) in the DROP group, with no difference observable to the progression to treatment dropout. The total number of deaths was 64.3% higher in the DROP group, and seven (25%) were because of CV death. As expected, cardiovascular deaths were not observed in the REG group.

In the evaluation of laboratory results (Fig. 2), we observed no mean differences at baseline between the groups. However, we found a decrease in CT (27.77 mg/dL, $p = 0.005$) and an increase in HDL-c (6.42 mg/dL, $p = 0.042$) serum levels in the REG group between baseline (T1) and a second evaluation made after 7 years (T2). None of these

Table 1 General characteristics of the study participants, previous events at baseline, and comparisons between the REG group, who maintained medical visits from 2012 to 2018, and the DROP group, who underwent medical visits in 2012 but did not continue regular treatment until 2018

Variables	Total (n = 92)	REG (n = 64)	DROP (n = 28)	p-Value
Data				
Age (years)	67 (IQR = 9.25)	67 (IQR = 10.25)	66 (IQR = 6.75)	0.489
Men—n (%)	50 (54.3%)	33 (51.6%)	17 (60.7%)	0.560
Women—n (%)	42 (45.7%)	31 (48.4%)	11 (39.3%)	0.607
Elderly (≥ 65 years)—n (%)	54 (58.7%)	37 (57.8%)	17 (60.7%)	0.976
Demographic data				
Marital status (married)—n (%)	50 (54.3%)	35 (54.7%)	15 (53.6%)	0.181
Schooling (complete elementary school)—n (%)	23 (25%)	14 (21.9%)	9 (32.1%)	0.632
Occupation (active)—n (%)	49 (53.3%)	29 (45.3%)	20 (71.4%)	0.002
Race/color (white)—n (%)	54 (58.7%)	41 (64.1%)	13 (46.4%)	0.434
Anthropometric data				
Weight (kg)	75 (IQR = 17.88)	73 (IQR = 16.4)	80 (IQR = 15.75)	0.024
BMI (kg/m^2)	28.25 (IQR = 5.32)	28.1 (IQR = 5.3)	28.7 (IQR = 4.67)	0.959
SBP (mmHg)	136 (IQR = 23)	140 (IQR = 23)	130 (IQR = 22.5)	0.238
DBP (mmHg)	80 (IQR = 10)	80 (IQR = 10)	80 (IQR = 10)	0.969
Clinical data				
Smoking—n (%)	28 (30.4%)	15 (23.4%)	13 (46.4%)	0.055
Physical exercise—n (%)	15 (16.3%)	13 (20.3%)	2 (7.1%)	0.276
Hypertension—n (%)	86 (93.5%)	58 (90.6%)	28 (100%)	0.246
T2DM—n (%)	69 (75%)	52 (81.2%)	17 (60.7%)	0.064

Values are expressed as n (%) or median ± IQR. Mann–Whitney U test, chi-square test

IQR interquartile range, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, T2DM type 2 diabetes mellitus

Significant difference $p < 0.05$

differences were observed in the DROP group. We observed an increase in HDL-c (11.40 mg/dL, $p = 0.013$) serum levels in the REG group compared with the DROP group in T2. We did not observe significant changes in LDL-c levels (T1 × T2) in the REG group: 115 mg/dL (IQR = 59.5) × 94.5 mg/dL (IQR = 42.75) or in the DROP group: 91 mg/dL (IQR = 67.25) × 88 mg/dL (IQR = 62). We found no mean differences for triglycerides, fasting glycemia, HbA1c, CRP, or CPK serum levels between evaluations in either group (Table 4).

Table 2 Association between previous events at baseline and groups; REG group, who maintained medical follow-up from 2012 to 2018, and the DROP group, who underwent medical consultations in 2012 but did not continue regular follow-up until 2018

Variables	Total ($n = 92$)	REG ($n = 64$)	DROP ($n = 28$)	OR (CI 95%)[a]	p-Value
Previous events					
Previous disease—n (%)	67 (72.8%)	45 (70.3%)	22 (78.6%)	0.27 (0.01–5.05)	0.768
AMI—n (%)	45 (48.9%)	30 (46.9%)	15 (53.6%)	33.63 (2.09–541.42)	0.026
PTCA—n (%)	25 (27.2%)	16 (25%)	9 (32.1%)	1.56 (0.19–12.87)	1
MCRS—n (%)	33 (35.9%)	20 (31.2%)	13 (46.4%)	4.67 (0.56–39.03)	0.309
CHF—n (%)	32 (34.8%)	14 (21.9%)	18 (64.3%)	103.64 (2.38–4511.47)	0.031
DCM—n (%)	9 (9.8%)	5 (7.8%)	4 (14.3%)	0.15 (0.01–2.99)	0.431
Aneurysm—n (%)	1 (1.1%)	1 (1.6%)	0 (0%)	NC	NC
Arrhythmias—n (%)	21 (22.8%)	8 (12.5%)	13 (46.4%)	90.76 (0.81–10,108.47)	0.121
History of angina—n (%)	43 (46.7%)	29 (45.3%)	14 (50%)	1.84 (0.24–14.06)	1

Values are expressed as n (%)

AMI acute myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty, *MCRS* myocardial revascularization surgery, *CHF* congestive heart failure, *DCM* dilated cardiomyopathy, *NC* not calculated

Significant association $p < 0.05$

[a]OR: Adjusted Odds Ratio, where age, sex, schooling years, marital and working status, body mass index (BMI), established T2DM, and auto-declared skin color were included in multiple binomial (logit link function) generalized linear models

DISCUSSION

Despite the higher number of visits/year in the DROP group, we observed an increased hazard of AMIs by follow-up time in the DROP group compared with the REG group ($p < 0.001$). In addition, previous AMI was also associated with progression to treatment dropout ($p < 0.05$). Thus, patients who are noncompliant with follow-up visits are those who experience more events. In fact, although patients with DLP should already be considered at high CV risk, the presence of additional risk factors, such as T2DM and other chronic conditions, amplifies the risk of CVD [10]. It is estimated that coronary events, fatal or not, occur in approximately 50% of men diagnosed with DLP before the age of 50 years and in 30% of women diagnosed before the age of 60 years [10–13]. In addition, the literature indicates that the average age at CVD presentation is approximately 43 years in

men and 52 years in women [13]. It is known, however, that when patients with DLP and multiple comorbidities receive adequate treatment and achieve therapeutic goals, their risk of developing CVD is similar to that of the general population [13, 14]. A randomized trial showed that intensive patient care improved patient adherence and decreased serum CT and LDL-c levels [11]. The improvements in patient adherence and blood lipid levels were consistent with the results of randomized clinical trials with a follow-up of more than 6 months [5–8]. Although we did not find an improvement in LDL-c for either group, there was a similar trend in our study for CT and HDL-c in the REG group. We observed a significant improvement in laboratory parameters (REGT1 × REGT2) for a decrease in CT and an increase in HDL-c ($p < 0.05$). We did not observe significant mean differences for the DROP group. In the intergroup mean difference

Table 3 Risk factors associated with treatment dropout based on medications used at baseline

Variable	Total ($n = 92$)	REG ($n = 64$)	DROP ($n = 28$)	OR (CI 95%)[a]	p-Value
Drug					
Beta blockers—n (%)	80 (87%)	55 (85.9%)	25 (89.3%)	8 (0.05–1269.03)	0.842
CCBs—n (%)	25 (27.2%)	20 (31.2%)	5 (17.9%)	0.13 (0.01–1.49)	0.201
ACEIs—n (%)	31 (33.7%)	16 (25%)	15 (53.6%)	73.79 (1.65–3296.87)	0.052
ARBs—n (%)	41 (44.6%)	31 (48.4%)	10 (35.7%)	0.57 (0.1–3.42)	0.596
Statins—n (%)	81 (88%)	58 (90.6%)	23 (82.1%)	0.16 (0.01–2.58)	0.396
Anticoagulants—n (%)	9 (9.8%)	9 (14.1%)	0 (0%)	NC	NC
Antiplatelets—n (%)	59 (64.1%)	37 (57.8%)	22 (78.6%)	3.22 (0.47–21.98)	0.464
Diuretics—n (%)	54 (58.7%)	31 (48.4%)	23 (82.1%)	43.33 (2.23–841.39)	0.025
Ezetimibe—n (%)	30 (32.6%)	28 (43.8%)	2 (7.1%)	0.08 (0.01–0.93)	0.088
Fibrates—n (%)	18 (19.6%)	10 (15.6%)	8 (28.6%)	320.01 (3.97–25809.74)	0.020
Antiarrhythmics—n (%)	20 (21.7%)	8 (12.5%)	12 (42.9%)	5.81 (0.46–73.37)	0.347
Oral hypoglycemics—n (%)	28 (30.4%)	22 (34.4%)	6 (21.4%)	0.24 (0.03–2.09)	0.389
Glinides—n (%)	16 (17.4%)	13 (20.3%)	3 (10.7%)	0.3 (0.01–7.94)	0.945
Metformin—n (%)	45 (48.9%)	32 (50%)	13 (46.4%)	2.86 (0.18–46.43)	0.921
Insulin—n (%)	16 (17.4%)	11 (17.2%)	5 (17.9%)	0.95 (0.1–9.45)	1
Allopurinol—n (%)	17 (18.5%)	8 (12.5%)	9 (32.1%)	18.9 (0.63–566.39)	0.180
Adrenergic agonists—n (%)	3 (3.3%)	2 (3.1%)	1 (3.6%)	NC	NC
Nitrates—n (%)	31 (33.7%)	19 (29.7%)	12 (42.9%)	6.11 (0.65–57.24)	0.225

Values are expressed as n (%). Absolute frequency (relative)

ACEIs angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *CCBs* calcium channel blockers, *NC* not calculated

Significant difference $p < 0.05$

[a]OR adjusted odds ratio, where age, sex, BMI, ethnicity, marital status, occupation, established T2DM, and schooling years were included in multiple binomial models

comparison (REGT2 × DROPT2) an increase in HDL-c was the only exception, with a significant improvement in the evaluation of laboratory results with follow-up time ($p < 0.05$). Interestingly, despite this lack of significant laboratory changes, we observed that the DROP group completed more consultations/year than the REG group, possibly because the patients in the DROP group had a higher CV risk ($p = 0.007$).

Another interesting finding was the high prevalence of T2DM in the study population. The reported prevalence of T2DM in the adult population is 12% [1]; however, in our study, this prevalence was 75%, identified by HbA1c values greater than or equal to 6.5%. The importance of long-term drug treatment for patients with T2DM has been demonstrated in several randomized clinical trials [5–8]. Reducing blood glucose in high-risk CV patients with prediabetes or T2DM is essential [7]. Glycemia is

Table 4 Laboratory variables at baseline (T1) and second evaluation made after follow-up time (T2) with comparison between groups: the REG group who maintained medical visits from 2012 to 2018, and the DROP group, who underwent medical visits in 2012 but did not continue regular treatment until 2018

Variable	Overall (T1)	REG (T1)	DROP (T1)	REG (T2)	DROP (T2)	*p*-Value
CT (mg/dL)	173 (IQR = 71)	193 (IQR = 73.75)	182 (IQR = 95.5)	166 (IQR = 54.25)	162.5 (IQR = 57.75)	0.032
LDL-c (mg/dL)	98.5 (IQR = 53)	115 (IQR = 59.5)	91 (IQR = 67.25)	94.5 (IQR = 42.75)	88 (IQR = 62)	0.209
HDL-c (mg/dL)	40 (IQR = 15.25)	41 (IQR = 14.5)	33 (IQR = 14.75)	44.5 (IQR = 19)	39.5 (IQR = 16)	0.001
Triglycerides (mg/dL)	146 (IQR = 105.75)	139 (IQR = 115.25)	171 (IQR = 256)	147 (IQR = 94.25)	145.5 (IQR = 102.75)	0.202
Fasting glucose (mg/dL)	109.5 (IQR = 52)	110 (IQR = 48)	126.5 (IQR = 49.75)	104.5 (IQR = 62.25)	108.5 (IQR = 38.25)	0.403
CRP (mg/dL)	0.21 (IQR = 0.6)	0.13 (IQR = 0.33)	0.69 (IQR = 0.82)	0.2 (IQR = 0.35)	0.4 (IQR = 0.59)	0.003
CPK (U/L)	109 (IQR = 104)	107 (IQR = 109.75)	131.5 (IQR = 178)	115 (IQR = 59.75)	87 (IQR = 144.5)	0.704
HbA1c (%)	6.59 (IQR = 2)	6.5 (IQR = 1.75)	6.6 (IQR = 2.71)	6.5 (IQR = 2.15)	6.75 (IQR = 1.75)	0.773

Values are expressed as median $\pm$ IQR

IQR: interquartile range, *CT* total cholesterol, *LDL-c* low-density lipoprotein, *HDL-c* high-density lipoprotein, *HbA1c* glycated hemoglobin, *CPK* creatine phosphokinase, *CRP* C-reactive protein

Significant difference $p < 0.05$

a strong and independent predictor of long-term mortality in patients with CVD, and intensive blood glucose control is necessary [14]. Despite this, in our study we did not observe significant mean differences in HbA1c levels after follow-up in either group, including 6.5% (IQR = 2.15) in the REG group and 6.75 (IQR = 1.75) in the DROP group. However, even though no laboratory improvement was observed, regular multidisciplinary treatment of patients with T2DM was associated with reduced CV risk compared with routine care in the first 5 years after diagnosis [5–8]. Interestingly, we observed that patients in the REG group had greater adherence to multidisciplinary treatment compared with patients in the DROP group ($p < 0.001$).

The benefit of statin therapy is also related to the overall risk and intensity of treatment [15]. Patients with T2DM have a higher CV risk than those without T2DM; high-intensity statin therapy is preferred for patients with T2DM [14, 16, 17]. However, no randomized clinical trial of treatment with high-intensity statins has been conducted in cohorts exclusively comprising patients with T2DM. In our study, statins were the most commonly used drugs; they showed similar use between groups [aOR = 0.16 (0.01–2.42)] and were used by 88% of patients, many of whom were considered high risk, having experienced CV events prior to our study (72.8%). Greater adherence to drug therapy is associated with lower mortality and lower CV morbidity [3, 10, 11]. In a meta-analysis, therapy associated with a 50% decrease in LDL-c led to a 15% reduction in CV outcomes [18]. In fact, we observed a trend towards greater use of statins by the REG group (90.6%) than by the DROP group (82.1%) ($p = 0.069$). However, we did not observe any association of risk or protection for statin treatment dropout ($p = 0.372$). Early medical interventions and a greater number of consultations offer promise as a potential method for addressing this important care gap to maximize the acceptance of treatment [19]. Higher adherence to drug therapy is associated with lower mortality, lower CV morbidity, and lower costs to the health system [3, 12, 13]. Although we did not assess adherence to drug therapy in our study, we observed that the use of some medications, such as fibrates and diuretics, were listed as a major risk factor for treatment dropout ($p < 0.05$).

The presence of previous CV events is also related to lower adherence to long-term drug therapy, and approximately 50% of patients
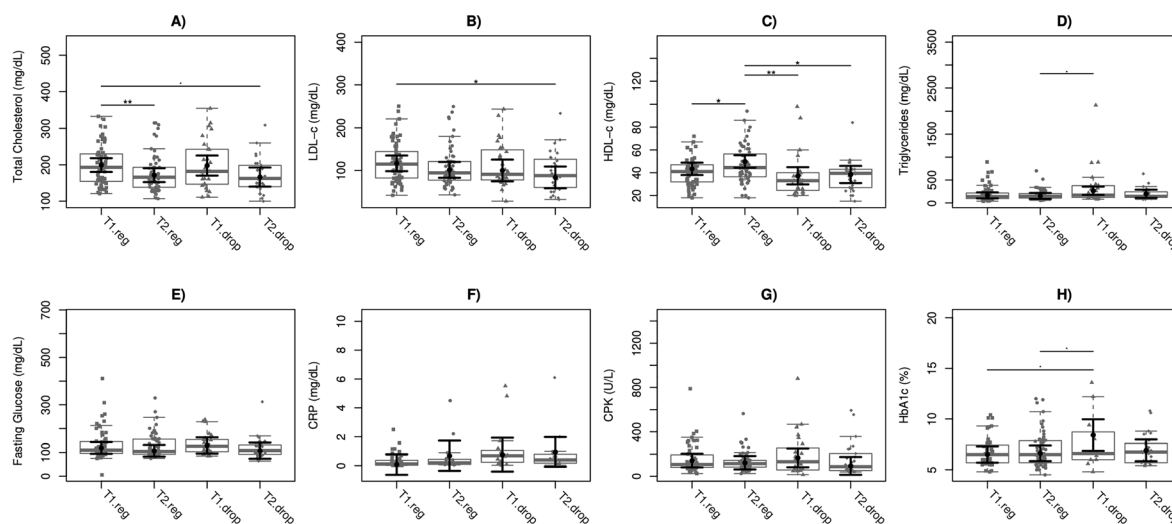
Fig. 2 Laboratory intergroup comparison (REG × DROP) at T2 and T1. The box-plot and strip plot of **A** CT, **B** LDL-c, **C** HDL-c, **D** triglycerides, **E** fasting glucose, **F** CRP, **G** CPK, and **H** HbA1c values in the REG and DROP groups at T1 and T2 are represented in gray. The black central circle represents the expected average marginal effect for each group estimated with linear fixed effects models. The fixed effects of the models were the group (REG or DROP), the evaluation time point (T1 or T2), and the first-order interaction between the previous models. The confounding effects included in all models were sex, age, BMI, color/race, education, established T2DM, marital status, and working versus unemployed status. The black horizontal bars represent the 95% confidence intervals of the expected mean marginal effects for each group. The *p*-values were corrected for the number of contrasts/two-by-two comparisons using Tukey's honest significant difference (HSD) method. The following values were considered significant: $^*p < 0.05$; $^{**}p < 0.01$. Differences were considered suggestive when $p < 0.1$

discontinue medication 12 months after a CV event [12]. In our study, patients with the presence of previous events of both AMI and CHF had a greater chance of not adhering to follow-up clinic management than those who had not experienced these events previously ($p < 0.05$).

There is growing evidence of lower overall mortality in patients who are treated by a multidisciplinary team at specialized outpatient services for DLP and T2DM versus primary care treatment [11, 20, 21]. A large study with a European population showed that after 5 years of intensive treatment compared with basic treatment, there was a greater reduction in CV risk factors [5–11]. There was also an increase in the prescription of medications and a 17% reduction in CV outcomes [11]. Interestingly, as already mentioned, we observed a higher number of medical visits per follow-up time point in the DROP group [aOR = 4.36

(3.95–4.81)] than in the REG group [aOR = 3.38 (3.2–3.57)] ($p = 0.007$). However, the number of consultations with a nutritionist was significantly higher in the REG group (76.6%) than in the DROP group (28.6%) by follow-up time, showing greater adherence to multidisciplinary treatment. ($p < 0.001$). Thus, we cannot disregard the possibility that a reduced hazard in CV outcomes is related to greater adherence to multidisciplinary treatment with physicians and nutritionists.

Our study has some limitations including the sample size, which is relatively small, and findings could be due to selection bias. The DROP group only has half the patients compared with the REG group, which may be one reason we did not find a significant difference between the two groups in the CV outcomes.

CONCLUSION

The analysis of CV outcomes of the studied population provides a greater understanding of the importance of a multidisciplinary treatment. There seems to be a reduced hazard in CV events, especially AMI, in patients who undergo regular treatment, even without major laboratory mean differences compared with dropout patients. We observed that adherence to multimodal clinical treatment can be negatively impacted by the patient's previous clinical condition and the profile of drugs used. This presents greater possibilities for long-term clinical applications since preventive and outpatient medical monitoring has low risk, is affordable, and may represent an additional measure to incorporate into patient treatment.

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