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Digital Intervention to Optimize LDL-C and Lipid Management in Patients at High and Very High Cardiovascular Risk: The Findings of the REMEXDIS Study in Real-World Clinical Practice

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Abstract

Inadequate management of low-density lipoprotein cholesterol (LDL-C) in patients at high and very high cardiovascular risk remains a major clinical challenge due to poor adherence, therapeutic inertia, and limited follow-up. Digital tools may improve adherence, prompt treatment intensification, and increase attainment of lipid targets. We evaluated the REMEXDIS mobile app in a prospective, comparative, multicenter, real-world, quasi-experimental study with 12 months' follow-up among adults at high or very high cardiovascular risk treated at Mexican Social Security Institute facilities. Materials and methods: Participants voluntarily downloaded the app, which provided reminders, personalized feedback, and physician alerts when LDL-C exceeded targets. Longitudinal changes among app users were assessed over 12 months, and 12-month LDL-C outcomes were additionally compared between app users and a contemporaneous non-app comparison group using multivariable adjusted analyses. Results: Median age was 64 years and 54.3% were female. Among 14,497 app users with paired baseline and 12-month data, median LDL-C decreased from 60 to 48 mg/dL, while LDL-C target attainment increased from 55.4% to 77.5%. In the high-risk subgroup, target attainment increased from 61.3% to 85.8%, and in the very-high-risk subgroup from 48.9% to 68.4%. Monotherapy decreased from 84.2% to 54.0%, whereas dual therapy increased from 13.4% to 43.8%. In adjusted analyses, app use was associated with an 11.53 mg/dL lower LDL-C level at 12 months compared with non-app use (95% CI, 10.08–12.98; $p < 0.01$) and with higher odds of achieving the LDL-C target at 12 months (adjusted OR 2.89, 95% CI, 2.54–3.28; $p < 0.01$).

Academic Editor: Rüdiger Pryss

Received: 19 August 2026
Revised: 18 September 2026
Accepted: 21 September 2026
Published: 24 September 2026

Conclusions: In this large real-world cohort, REMEXDIS app use was associated with more favorable 12-month LDL-C levels and target attainment after multivariable adjustment. However, because app use was not randomized, these findings should be interpreted as associations rather than causal effects. Further studies are needed to evaluate long-term clinical outcomes, cost-effectiveness, and the contribution of specific components of the digital intervention.

Keywords: dyslipidemia; mobile health; cardiovascular prevention

1. Introduction

Cardiovascular disease is the leading cause of death worldwide, largely due to dyslipidemia and, particularly, elevated levels of low-density lipoprotein cholesterol (LDL-C), for which inadequate management continues to be challenging in routine clinical practice [1]. Despite the availability of effective lipid-lowering therapies, a significant proportion of patients at high and very high risk do not achieve established treatment targets because of factors such as poor adherence, therapeutic inertia, and limited follow-up. Approximately 26.5% of patients at high and very high risk are reported to achieve the recommended LDL-C targets, indicating suboptimal use of targeted therapies [2]. Recently, mobile health technologies have emerged as promising tools for strengthening education, improving adherence, and facilitating continuous monitoring. In this way, their use demonstrates benefits across various areas of cardiovascular prevention [3]. Structured digital interventions targeting both patients and clinical staff have also been shown to improve the intensification of treatment and optimize the implementation of guidelines, making them an innovative strategy for improving lipid management across various healthcare systems [4,5].

In this setting, the REMEXDIS mobile app was designed to support clinical monitoring, promote LDL-C target attainment, and facilitate timely therapeutic decision-making through patient-directed support and physician alerts. The present study evaluated the association between app use and 12-month lipid management in a large, multicenter, real-world cohort of patients at high or very high cardiovascular risk treated across different levels of care within the Mexican Social Security Institute. Beyond the use of a mobile application itself, the contribution of REMEXDIS lies in its large-scale implementation in routine clinical practice and in the longitudinal assessment of LDL-C control and treatment transitions. The baseline characteristics of the REMEXDIS cohort will be reported separately in another publication.

2. Materials and Methods

2.1. Study Design

This was a prospective, comparative, real-world, quasi-experimental study of adults at high and very high cardiovascular risk. Participants attending outpatient family medicine or specialty clinics (internal medicine, cardiology, or endocrinology) were invited at the baseline visit to download and use the REMEXDIS mobile app; app use was voluntary and at the patient's discretion. Clinical, biochemical, and treatment variables were recorded at baseline and during the 12-month follow-up. Longitudinal changes in lipid parameters, LDL-C target attainment, and treatment patterns were evaluated among app users. In addition, 12-month LDL-C outcomes were compared between app users and participants who did not use the app, who constituted a contemporaneous non-app

comparison group. Because app use was not randomized, the non-app participants were not considered a randomized control group.

2.2. Scope, Hospitals, and Groups

The centers were selected through an open invitation issued by high-specialty medical units and decentralized administrative bodies for applications, which encouraged participation among medical staff. Hospitals from all three levels of care in the Northern, Western, Central, and Southeastern regions were included, in accordance with the regional classification of the Mexican Social Security Institute.

Eligible participants were adults aged 18 years or older, of either biological sex, who fulfilled the predefined REMEXDIS operational criteria for high or very high cardiovascular risk, as detailed in the operational definitions below. Patients who were hospitalized at screening, had experienced acute coronary syndrome within the previous 2 months, or were pregnant or breastfeeding were excluded.

2.3. Treatment and Procedures

Once eligibility was confirmed and written informed consent was obtained, standardized interviews and clinical evaluations were conducted at the outpatient clinic. Lipid levels were determined using a portable test strip analyzer, with an intra-assay variability of 3.3% to 3.4% and an inter-assay variability of 3.7% to 4.8%; these values are considered acceptable for outpatient settings [6].

During the baseline visit, patients were invited to download the mobile app that was designed for the REMEXDIS study onto their cell phones free of charge. Although patients used the app entirely at their discretion, at each follow-up visit the research team encouraged them to download and use it through reminders and direct guidance.

The app was designed and developed by the investigators leading the study to facilitate clinical monitoring and help patients with dyslipidemia who were at high or very high cardiovascular risk to achieve their LDL-C treatment targets. Using push notifications, the system sends personalized messages: a congratulatory message when the patient reaches their LDL-C target and an alert when their levels are outside the recommended range. In the latter case, an electronic notification is also sent to the treating physician to inform them of the deviation from the target. Notifications are sent every 30 days or updated based on new laboratory test results. The app also includes automatic reminders for medical appointments (30 days and 48 h in advance) and a customizable calendar; these enable patients to set personalized reminders for taking medication or other activities related to their care.

Representative screenshots of the REMEXDIS app's home screen, calendar module, and notification history are provided in Supplementary Figure S1.

The app was developed using Vue.js v3.0 (Vue.js Core Team, 2014; available from: https://vuejs.org/guide/introduction.html; accessed on 29 April 2026) for Android devices and SwiftUI (Apple Inc., Cupertino, CA, USA) for iOS. It is approximately 16 MB in size. The app is available for free download from official app stores. However, functional access is restricted to active REMEXDIS participants. After installation, users are required to enter their Mexican Social Security Number (Número de Seguridad Social, NSS), which is automatically verified against the REMEXDIS study database. Access to the app's study-specific functions is granted only when the NSS corresponds to an authorized REMEXDIS participant. This authentication procedure was implemented to ensure confidentiality and protect participants' personal and clinical data.

In summary, app download, activation, and use were supervised by authorized healthcare personnel and the monitoring team; access was limited to eligible participants who had provided written informed consent, and clinical alerts were generated only when

LDL-C values were entered during scheduled evaluations. Detailed information regarding the app's copyright, commercial notice, and trademark registration status is provided in the Supplementary Materials.

All participants were monitored for 12 months, starting from the baseline visit. Patients underwent periodic assessments and the collection of clinical and biochemical data at each follow-up visit.

The data were entered into electronic forms, with manual supplementation when necessary, and synchronized with a secure central server at the High-Specialty Medical Units Specialty Hospital No. 1, CMN Bajío Mexican Social Security Institute with access control and traceability. The staff underwent 2 weeks of training and standardization in measurement techniques and procedures; a contract research organization monitored operational compliance.

2.4. Variables and Operational Definitions

The variables and their operational definitions are described in Table 1.

Table 1. Variables and operational definitions used in the REMEXDIS study.

Atherosclerotic cardiovascular disease	Confirmed history of at least one of the following conditions: (a) myocardial infarction (fatal or nonfatal), angina pectoris, and/or heart failure; coronary revascularization (either surgical or percutaneous); (b) cerebrovascular disease such as embolism, stroke, or nontraumatic hemorrhage, and/or transient ischemic attack; (c) peripheral arterial disease, aortic disease, and/or thoracic or abdominal aortic aneurysm [7].
High cardiovascular risk	Presence of at least one of the following conditions: cholesterol level ≥ 310 mg/dL (8 mmol/L) and or LDL-C level ≥ 190 mg/dL and or blood pressure ≥ 180/110 mmHg; familial hypercholesterolemia in first- or second-degree relatives without other risk factors; diabetes mellitus without target organ damage or lasting more than 10 years, plus another risk factor such as hypertension, dyslipidemia, or active smoking; chronic kidney disease with a glomerular filtration rate of between 30 and 59 mL/min [7].
Very high cardiovascular risk	Recurrent atherosclerotic disease; or atherosclerotic cardiovascular disease plus any of the following: type 1 or type 2 diabetes mellitus lasting >20 years; chronic kidney disease with a glomerular filtration rate < 30 mL/min; dialysis or hemodialysis; or family history of hypercholesterolemia in first- or second-degree relatives [7].
Lipid-lowering therapy	Treatment involving the use of statins (atorvastatin, pravastatin, rosuvastatin, simvastatin), the selective inhibitor of the Niemann–Pick C1-like 1 (NPC1L1) intestinal cholesterol transporter (ezetimibe), and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (evolocumab) as well as regimens involving monotherapy, dual therapy or triple therapy.
Dyslipidemia	Condition characterized by elevated blood lipid levels, which increases the risk of cardiovascular disease, as determined solely by the patient's self-reported medical history or by a diagnosis recorded in the medical record.
Lipid targets or achieved LDL-C targets	The target was set at an LDL-C of <70 mg/dL for patients classified as being at high risk and <55 mg/dL for patients classified as being at a very high risk.
Analysis populations	The full cohort comprised 17,532 participants, including 15,346 app users and 2186 non-app participants. Longitudinal within-patient

	analyses included app users with paired baseline and 12-month data (n = 14,497) and evaluated changes in lipid profiles, LDL-C target attainment, and lipid-lowering treatment. Comparative analyses included participants with evaluable 12-month LDL-C data (14,497 app users and 1291 participants in the contemporaneous non-app comparison group) and assessed the association between app use and 12-month LDL-C outcomes using multivariable-adjusted models.
Contract research organization (CRO)	For this study, the CRO was responsible for operational and methodological support limited to study monitoring and quality control.

2.5. Sample Size

Based on event rates reported in the FOURIER trial [8] (11.3% vs. 9.8%; α = 0.05; power, 80%), the required sample size was 13,166 participants. Considering an expected attrition rate of 30%, the minimum recruitment target was set at ≥17,116 participants; a detailed description of this calculation will be reported in a separate publication. A total of 17,532 participants were included in the REMEXDIS cohort. Of these, 15,346 used the REMEXDIS app and 2186 did not use the app. Longitudinal analyses of within-patient changes were conducted among app users, whereas comparative analyses of 12-month LDL-C outcomes included both app users and the contemporaneous non-app comparison group.

2.6. Ethical Considerations and Registration

All procedures were conducted in accordance with relevant institutional guidelines and regulations and were approved by the appropriate institutional review board. The protocol was approved by the National Committee for Scientific Research (approval number R-2021-785-103) on 14 February 2022 and registered on ClinicalTrials.gov (registration number NCT05542719). Each facility obtained local authorization. All participants provided written informed consent prior to enrollment in the study. The data were handled confidentially and in an encrypted manner, in accordance with the Declaration of Helsinki, local regulations, and good clinical practice.

2.7. Statistical Methods

A descriptive analysis was conducted of all the study variables. Categorical variables (e.g., sex and cardiovascular risk factors) are expressed as absolute frequencies and proportions. Continuous variables (such as age and serum lipid concentrations) are reported as medians and percentiles because they did not follow a normal distribution.

Within-patient changes between baseline and the 12-month follow-up were evaluated using the Wilcoxon signed-rank test for continuous variables. Changes in paired binary outcomes, including LDL-C target attainment, were evaluated using McNemar's test. A two-sided p-value < 0.05 was considered statistically significant.

Changes in paired multicategorical lipid-lowering therapy regimens between baseline and the 12-month follow-up were evaluated using the McNemar–Bowker test of symmetry.

To assess the association between app use and LDL-C levels at 12 months, a multivariable analysis of covariance (ANCOVA) was performed, with 12-month LDL-C as the dependent variable and app use as the main independent variable. The model was adjusted for baseline LDL-C, age, sex, body mass index, diabetes mellitus, systemic hypertension, chronic kidney disease, active smoking, cardiovascular risk category, and level of care. Adjusted between-group differences with 95% confidence intervals (CIs) were reported.

To assess the association between app use and LDL-C target attainment at 12 months, a multivariable binary logistic regression model was performed. The dependent variable was achievement of the LDL-C target at 12 months, and app use was the main

independent variable. The model was adjusted for baseline LDL-C, baseline LDL-C target attainment, age, sex, body mass index, diabetes mellitus, systemic hypertension, chronic kidney disease, active smoking, cardiovascular risk category, and level of care. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Given the differential availability of 12-month follow-up data between app users and non-app users, a sensitivity analysis using inverse-probability-of-observation weighting was performed. The probability of having evaluable 12-month LDL-C data was estimated using a multivariable logistic regression model including app use, baseline LDL-C, baseline LDL-C target attainment, age, sex, body mass index, diabetes mellitus, systemic hypertension, chronic kidney disease, active smoking, cardiovascular risk category, and level of care. Inverse probability weights were calculated as the reciprocal of the estimated probability of 12-month evaluability and applied to the outcome models. Weighted analyses were performed as sensitivity analyses to assess the robustness of the primary complete-case findings to differential follow-up.

All statistical analyses were performed using IBM SPSS® Statistics for Windows, version 31 (IBM Corp., Armonk, NY, USA) and MedCalc®, version 23.3.7 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

A total of 17,532 patients at high or very high cardiovascular risk were included in the REMEXDIS cohort. Of these, 15,346 (87.5%) used the REMEXDIS mobile app and 2186 (12.5%) did not use the app, constituting a contemporaneous non-app comparison group. The primary longitudinal analyses of changes in lipid profiles, LDL-C target attainment, and lipid-lowering treatment patterns were conducted among app users, whereas the association between app use and 12-month LDL-C outcomes was additionally evaluated by comparing app users with non-app users using multivariable adjusted analyses. Twelve-month LDL-C data were available for 14,497 app users and 1291 non-app users. Participant disposition and availability of 12-month follow-up data are presented in Figure 1.

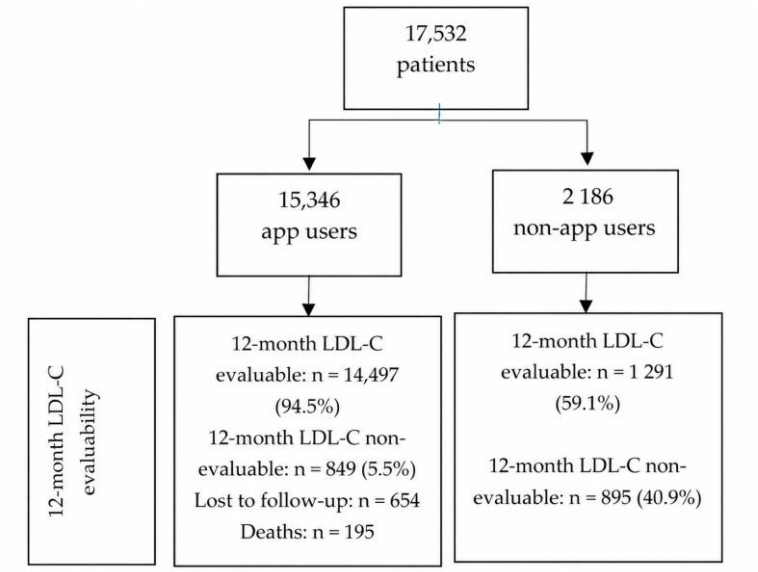

Figure 1. Participant flow and 12-month LDL-C evaluability according to REMEXDIS app use.

3.1. Baseline Characteristics

Among the 15,346 app users, the median age was 64 years (25th–75th percentile, 55–72 years), and 54.3% were female. The population had a substantial burden of cardiometabolic comorbidities, particularly systemic hypertension and diabetes mellitus, and included a clinically relevant subgroup of patients with familial hypercholesterolemia (Table 2).

Table 2. Baseline demographic characteristics and clinical comorbidities of app users.

Variable	Baseline *n* = 15,346
Age, years, median (25th–75th percentile)	64 (55–72)
Male, *n* (%)	7016 (45.7)
Female, *n* (%)	8330 (54.3)
Familial hypercholesterolemia, *n* (%)	1154 (7.5)
Smoking, *n* (%)	5116 (33.3)
Chronic kidney disease, *n* (%)	902 (5.9)
Diabetes mellitus, *n* (%)	10,025 (65.3)
Systemic hypertension, *n* (%)	10,328 (67.3)
Hypertriglyceridemia, *n* (%)	2193 (14.3)
Dyslipidemia, *n* (%)	7295 (47.5)

The results are expressed as medians and percentiles or absolute numbers, and percentages. *n*; absolute number, %; percentage.

3.2. Changes in Lipid Profiles and Treatments in the Overall Population of App Users

In the overall population of app users with paired baseline and 12-month data, median LDL-C decreased from 60 to 48 mg/dL during the 12-month follow-up, while LDL-C target attainment increased from 55.4% to 77.5%. Monotherapy decreased from 84.2% at baseline to 54.0% at 12 months, whereas dual therapy increased from 13.4% to 43.8%. Triple therapy increased from 1.2% to 2.0%, while the proportion of patients receiving no lipid-lowering treatment decreased from 1.2% to 0.2%. These changes occurred concurrently with a shift from monotherapy toward greater use of combination lipid-lowering therapy (Table 3; Figures 2a and 3a).

Table 3. Changes in lipid profile, LDL-C target attainment, and lipid-lowering therapy at 12 months among app users with paired baseline and 12-month data.

Variable	Baseline *n* = 14,497	12-Month Follow-Up Visit *n* = 14,497	Delta (Δ)	*p*-Value
Total cholesterol level, mg/dL, median (percentiles)	137 (118–160)	126 (110–144)	−12 (−38 to 12)	<0.01
Triglyceride level, mg/dL, median (percentiles)	161 (122–209)	153 (115–207)	−6 (−69 to 55)	<0.01
HDL-C, mg/dL level, median (percentiles)	39 (33–50)	42 (36–52)	3 (−9 to 14)	<0.01
LDL-C, mg/dL level, median (percentiles)	60 (46–81)	48 (37–61)	−11 (−31 to 4)	<0.01
Total cholesterol-to-HDL-C ratio, median (percentiles)	3.42 (2.83–4.18)	2.90 (2.40–3.50)	−0.51 (−1.33 to 0.30)	<0.01
LDL-C target achieved, *n* (%)	8036 (55.4)	11,241 (77.5)	22.1 *	<0.01
Lipid-lowering therapy				
Monotherapy, *n* (%)	12,209 (84.2)	7832 (54.0)	−30.2 *	<0.01 †

Dual therapy, *n* (%)	1936 (13.4)	6345 (43.8)	30.4 *	-
Triple therapy, *n* (%)	171 (1.2)	297 (2.0)	0.9 *	-
No lipid-lowering treatment, *n* (%)	181 (1.2)	23 (0.2)	−1.1 *	-

Continuous variables are expressed as median (25th–75th percentile). For continuous variables, Δ represents the within-patient change from baseline to the 12-month follow-up (12-month value minus baseline value), summarized as median (25th–75th percentile). Continuous variables were compared using the Wilcoxon signed-rank test. LDL-C target attainment was compared using McNemar's test. Changes in lipid-lowering therapy categories were evaluated using the McNemar–Bowker test of symmetry. For categorical variables, Δ represents the absolute change in percentage points. Negative Δ values indicate a decrease from baseline, whereas positive values indicate an increase. * Percentage points. † Global *p*-value from the McNemar–Bowker test. *n*, absolute number; %, percentage; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Among app users with evaluable 12-month data, 3631 of the 6461 patients who had not achieved their LDL-C target at baseline (56.2%) achieved the target at 12 months, whereas 426 of the 8036 patients who had achieved the target at baseline (5.3%) no longer met the target at 12 months. Overall, 7610 patients maintained target attainment and 2830 remained above target. The paired change in LDL-C target attainment was statistically significant (McNemar's test, $p < 0.01$). Treatment patterns also changed significantly between baseline and 12 months (McNemar–Bowker $\chi^2 = 3317.49$, df = 5, $p < 0.01$). Among the 12,209 patients receiving monotherapy at baseline, 6808 (55.8%) remained on monotherapy, 5292 (43.3%) were receiving dual therapy at 12 months, and 109 (0.9%) were receiving triple therapy. Among the 1936 patients receiving dual therapy at baseline, 976 (50.4%) remained on dual therapy, 17 (0.9%) were receiving triple therapy, and 943 (48.7%) were receiving monotherapy at 12 months.

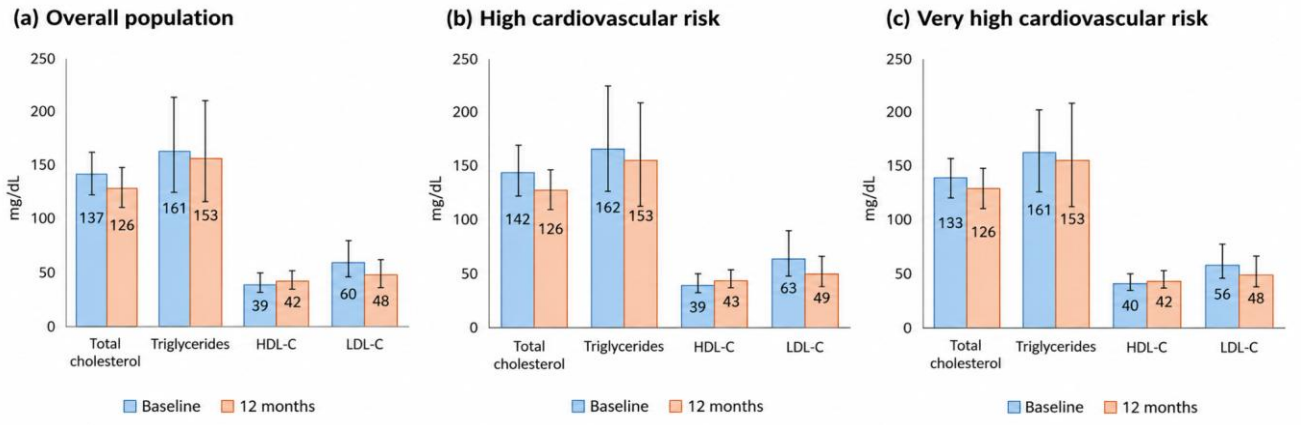

Figure 2. Lipid levels at baseline and at the 12-month follow-up among app users with paired data. Median values with 25th–75th percentiles are shown for (**a**) the overall population, (**b**) patients at high cardiovascular risk, and (**c**) patients at very high cardiovascular risk. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

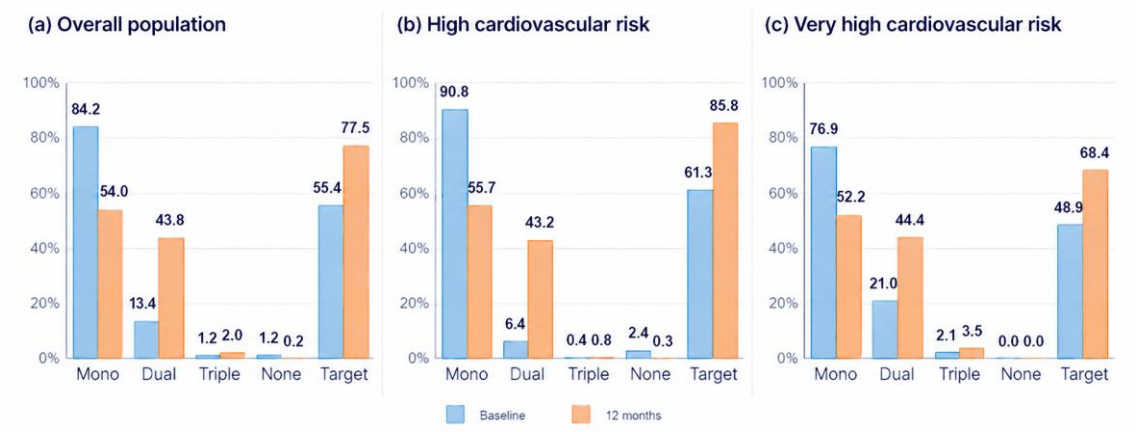

Figure 3. Changes in lipid-lowering therapy and LDL-C target attainment at 12 months among app users with paired baseline and 12-month data. Bar charts show the proportions of patients receiving monotherapy, dual therapy, triple therapy, no lipid-lowering treatment, and achieving the LDL-C target in (**a**) the overall population, (**b**) patients at high cardiovascular risk, and (**c**) patients at very high cardiovascular risk. LDL-C, low-density lipoprotein cholesterol.

3.3. Changes in Lipid Profiles and Treatments in Patients at High Risk Who Used the App

In the high-risk subgroup, median LDL-C decreased from 63 to 49 mg/dL during the 12-month follow-up, while LDL-C target attainment increased from 61.3% to 85.8%. Monotherapy decreased from 90.8% to 55.7%, whereas dual therapy increased from 6.4% to 43.2% and triple therapy from 0.4% to 0.8%. These changes occurred concurrently with a shift toward greater use of combination lipid-lowering therapy (Table 4; Figures 2b and 3b).

Table 4. Changes in lipid profile, LDL-C target attainment, and lipid-lowering therapy at 12 months among high-risk app users with paired baseline and 12-month data.

Variable	Baseline *n* = 7620	12-Month Follow-Up Visit *n* = 7620	Delta (Δ)	*p*-Value
Lipid profile				
Total cholesterol level, mg/dL, median (percentiles)	142 (122–167)	126 (111–144)	−16 (−43 to 8)	<0.01
Triglyceride level, mg/dL, median (percentiles)	162 (125–219)	153 (115–206)	−10 (−74 to 54)	<0.01
HDL-C level, mg/dL, median (percentiles)	39 (32–50)	43 (35–52)	3 (−9 to 14)	<0.01
LDL-C level, mg/dL, median (percentiles)	63 (47–88)	49 (37–61)	−15 (−36 to 2)	<0.01
Total cholesterol-to-HDL-C ratio, median (percentiles)	3.62 (2.91–4.44)	2.90 (2.39–3.50)	−0.67 (−1.58 to 0.22)	<0.01
LDL-C target				
LDL-C target achieved, *n* (%)	4673 (61.3)	6539 (85.8)	24.5 *	<0.01
Lipid-lowering therapy				
Monotherapy, *n* (%)	6922 (90.8)	4245 (55.7)	−35.1 *	<0.01 †
Dual therapy, *n* (%)	489 (6.4)	3294 (43.2)	36.8 *	-
Triple therapy, *n* (%)	28 (0.4)	58 (0.8)	0.4 *	-
No lipid-lowering treatment, *n* (%)	181 (2.4)	23 (0.3)	−2.1 *	-

Continuous variables are expressed as median (25th–75th percentile). For continuous variables, Δ represents the within-patient change from baseline to the 12-month follow-up (12-month value minus baseline value), summarized as median (25th–75th percentile). Continuous variables were compared using the Wilcoxon signed-rank test. LDL-C target attainment was compared using McNemar's test.

Changes in lipid-lowering therapy categories were evaluated using the McNemar–Bowker test of symmetry. For categorical variables, Δ represents the absolute change in percentage points. Negative Δ values indicate a decrease from baseline, whereas positive values indicate an increase. * Percentage points. † Global *p*-value from the McNemar–Bowker test. *n*, absolute number; %, percentage; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

3.4. Changes in Lipid Profiles and Treatments in Patients at Very High Risk Who Used the App

In the very-high-risk subgroup, median LDL-C decreased from 56 to 48 mg/dL during the 12-month follow-up, while LDL-C target attainment increased from 48.9% to 68.4%. Monotherapy decreased from 76.9% to 52.2%, whereas dual therapy increased from 21.0% to 44.4% and triple therapy from 2.1% to 3.5%. These changes occurred concurrently with a shift toward more intensive lipid-lowering regimens (Table 5; Figures 2c and 3c).

Table 5. Changes in lipid profile, LDL-C target attainment, and lipid-lowering therapy at 12 months among very-high-risk app users with paired baseline and 12-month data.

Variable	Baseline *n* = 6877	12-Month Follow-Up Visit *n* = 6877	Delta (Δ)	*p*-Value
Lipid profile				
Total cholesterol level, mg/dL, median (percentiles)	133 (115–152)	126 (110–144)	−8 (−32 to 15)	<0.01
Triglyceride level, mg/dL, median (percentiles)	161 (119–202)	153 (115–207)	−3 (−63 to 57)	0.07
HDL-C level, mg/dL, median (percentiles)	40 (34–50)	42 (36–52)	2 (−9 to 13)	<0.01
LDL-C level, mg/dL, median (percentiles)	56 (45–71)	48 (37–61)	−8 (−25 to 5)	<0.01
Total cholesterol-to-HDL-C ratio, median (percentiles)	3.26 (2.78–3.83)	2.89 (2.41–3.50)	−0.37 (−1.08 to 0.37)	<0.01
LDL-C target				
LDL-C target achieved, *n* (%)	3363 (48.9)	4702 (68.4)	19.5 *	<0.01
Lipid-lowering therapy				
Monotherapy, *n* (%)	5287 (76.9)	3587 (52.2)	−24.7 *	<0.01 †
Dual therapy, *n* (%)	1447 (21.0)	3051 (44.4)	23.3 *	-
Triple therapy, *n* (%)	143 (2.1)	239 (3.5)	1.4 *	-
No lipid-lowering treatment, *n* (%)	0 (0.0)	0 (0.0)	-	-

Continuous variables are expressed as median (25th–75th percentile). For continuous variables, Δ represents the within-patient change from baseline to the 12-month follow-up (12-month value minus baseline value), summarized as median (25th–75th percentile). Continuous variables were compared using the Wilcoxon signed-rank test. LDL-C target attainment was compared using McNemar's test. Changes in lipid-lowering therapy categories were evaluated using the McNemar–Bowker test of symmetry. For categorical variables, Δ represents the absolute change in percentage points. Negative Δ values indicate a decrease from baseline, whereas positive values indicate an increase. * Percentage points. † Global *p*-value from the McNemar–Bowker test. *n*, absolute number; %, percentage; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

3.5. Comparison Between App Users and Non-App Users

In the primary complete-case analysis, app use was associated with lower adjusted LDL-C levels at 12 months. In the multivariable ANCOVA adjusted for baseline LDL-C, age, sex, body mass index, diabetes mellitus, systemic hypertension, chronic kidney disease, active smoking, cardiovascular risk category, and level of care, adjusted mean LDL-

C at 12 months was 11.53 mg/dL lower among app users than among non-app users (95% CI, 10.08–12.98; $p < 0.01$).

In multivariable logistic regression analysis, app use was associated with higher odds of achieving the LDL-C target at 12 months (adjusted OR 2.89, 95% CI 2.54–3.28; $p < 0.01$), after adjustment for baseline LDL-C, baseline LDL-C target attainment, age, sex, body mass index, diabetes mellitus, systemic hypertension, chronic kidney disease, active smoking, cardiovascular risk category, and level of care.

3.6. Sensitivity Analysis Accounting for Differential Follow-Up

Twelve-month LDL-C data were available for 15,788 of the 17,532 participants (90.1%). Evaluability differed substantially according to app use, with 14,497 of 15,346 app users (94.5%) and 1291 of 2186 non-app users (59.1%) having evaluable 12-month LDL-C data ($p < 0.01$). To assess the potential impact of differential follow-up, an inverse-probability-of-observation weighted sensitivity analysis was performed. In the weighted ANCOVA, the adjusted between-group difference in 12-month LDL-C was 11.35 mg/dL in favor of app users, closely consistent with the 11.53 mg/dL difference observed in the primary complete-case ANCOVA. Similarly, in the weighted multivariable logistic regression model, app use remained associated with higher odds of LDL-C target attainment at 12 months (adjusted OR 2.75, 95% CI 2.47–3.05; $p < 0.01$), compared with an adjusted OR of 2.89 (95% CI 2.54–3.28; $p < 0.01$) in the primary complete-case analysis. Overall, the similarity of the weighted and unweighted point estimates indicated that the main findings were materially unchanged after accounting for differential 12-month evaluability.

4. Discussion

In this large real-world cohort of patients at high or very high cardiovascular risk, app users with paired baseline and 12-month data showed lower LDL-C levels, greater LDL-C target attainment, and a shift from monotherapy toward greater use of combination lipid-lowering therapy during follow-up. These changes were observed in both cardiovascular risk groups, although LDL-C target attainment remained lower among patients at very high risk. In adjusted analyses using the contemporaneous non-app comparison group, app use was associated with an 11.53 mg/dL lower LDL-C level at 12 months (95% CI, 10.08–12.98; $p < 0.01$) and higher odds of achieving the LDL-C target (adjusted OR 2.89, 95% CI, 2.54–3.28; $p < 0.01$). Sensitivity analyses accounting for differential 12-month evaluability yielded similar point estimates. Because app use was voluntary and nonrandomized, these findings should be interpreted as associations rather than evidence of a causal effect of the digital intervention.

Previous digital-health studies in lipid management have generally been conducted in smaller or more selected populations. Pongchaiyakul and Driessen randomized 150 patients with suboptimal adherence to lipid-lowering therapy over 12 weeks, primarily evaluating medication adherence and reporting favorable trends in lipid parameters [9]. Tekkeşin et al. randomized 483 patients at high cardiovascular risk and reported a significant reduction in the 1-year ASCVD risk score following a smartphone-based lifestyle intervention [10]. Among patients with acute coronary syndrome, Ruiz-Bustillo et al. evaluated 497 patients using a structured mobile-health intervention; 70.7% achieved LDL-C ≤ 70 mg/dL after the initial optimization period, and 71.1% of those with LDL-C measurements available at 1 year remained at or below this threshold [11]. Similarly, Chen et al. evaluated a health-information-technology-driven multidisciplinary strategy in 2001 patients with acute coronary syndrome and reported progressive improvement in 12-month LDL-C target attainment, from 53.8% to 64.2% across successive implementation years [12]. In comparison, REMEXDIS included 15,346 app users within a multicenter real-world healthcare network encompassing different levels of care, with 14,497 participants

having paired evaluable 12-month LDL-C data. LDL-C target attainment reached 77.5% at 12 months, accompanied by a substantial shift toward combination lipid-lowering therapy. Direct numerical comparisons across studies should be interpreted cautiously because of differences in patient populations, LDL-C targets, study designs, and intervention components. Nevertheless, the distinctive contribution of REMEXDIS lies in the large-scale implementation of a digital strategy integrating patient-directed support with physician-directed LDL-C alerts and the longitudinal assessment of lipid control and treatment transitions in routine clinical practice.

An important finding was the concurrent shift from monotherapy toward dual and triple lipid-lowering therapy, suggesting greater treatment intensification over the 12-month follow-up. A distinctive feature of the REMEXDIS app is its integration of patient-directed support, including medication and appointment reminders and personalized feedback, with physician-directed alerts when LDL-C values are outside the recommended target. These functions may facilitate clinical follow-up, timely review, and treatment intensification, consistent with previous evidence showing that electronic alerts and clinical decision-support systems can improve adherence to clinical guidelines [13–16]. However, medication adherence, frequency of app use, and physician responses to individual alerts were not objectively recorded. Therefore, the extent to which these specific components contributed to the observed treatment changes cannot be determined from the present study.

Although cardiovascular events were not a primary outcome of the present study, the improvement in LDL-C target attainment is clinically relevant because achieving and maintaining lower LDL-C levels is associated with a reduced risk of cardiovascular events [8,17]. This is particularly important in patients at very high cardiovascular risk, in whom persistent LDL-C elevation is associated with substantial residual cardiovascular risk. Therefore, the improvement in LDL-C target attainment observed during follow-up represents a clinically meaningful finding, although the present study was not designed to determine whether these changes translated into a reduction in cardiovascular events.

Although LDL-C target attainment improved in both cardiovascular risk groups, it remained lower among patients at very high risk than among those at high risk (68.4% vs. 85.8% at 12 months). This residual treatment gap is clinically relevant because patients at very high cardiovascular risk have more stringent LDL-C targets and frequently require intensive combination lipid-lowering therapy. Persistent failure to achieve recommended LDL-C targets in these patients has also been reported in European and Latin American real-world studies [18–20]. These findings emphasize the need for continued monitoring, timely treatment intensification, and individualized strategies for patients who remain above target despite structured follow-up.

5. Limitations of the Study

This study has several limitations. First, its real-world quasi-experimental design was not randomized, and app use was voluntary. The contemporaneous non-app group was therefore observational rather than randomly assigned, and differences between users and non-users may have influenced the results. Although the comparative analyses were adjusted for multiple clinical and demographic variables, selection bias, residual confounding, and confounding by unmeasured factors cannot be excluded. Consequently, the observed associations should not be interpreted as demonstrating a causal effect of the REMEXDIS app.

Second, 12-month evaluability differed substantially between app users and non-app users. Although inverse-probability-of-observation weighted sensitivity analyses yielded estimates similar to those from the primary complete-case analyses, this approach

accounts only for measured factors included in the evaluability model. Bias related to unmeasured determinants of follow-up availability may therefore remain.

Third, longitudinal changes in lipid-lowering treatment patterns were evaluated only among app users. Therefore, it cannot be determined whether the observed shift toward combination therapy was specifically associated with app use or reflected other factors, including routine clinical follow-up, temporal changes in medical care, or broader treatment-intensification practices.

Fourth, although the 12-month follow-up period was sufficient to assess changes in lipid parameters, LDL-C target attainment, and treatment patterns, it was insufficient to determine whether these changes translated into reductions in major cardiovascular events.

Fifth, objective app-engagement measures, including login frequency, interaction with push notifications, and physician responses to electronic alerts, were not systematically recorded. Medication adherence was also not objectively measured. Consequently, neither the relationship between the intensity of app use and clinical outcomes nor the contribution of individual app components could be evaluated.

Finally, despite standardized procedures and staff training, the multicenter collection of lipid measurements may have introduced intercenter variability and measurement-related information bias. Nevertheless, the study provides evidence from a large multicenter cohort treated under real-world clinical conditions.

6. Conclusions

In this large multicenter real-world cohort, use of the REMEXDIS app was associated with lower LDL-C levels and higher odds of LDL-C target attainment at 12 months after multivariable adjustment. Among app users with paired baseline and 12-month data, improvements in LDL-C levels and target attainment were accompanied by a shift from monotherapy toward more intensive combination lipid-lowering therapy. The comparative associations remained materially unchanged in sensitivity analyses accounting for differential follow-up. However, because app use was voluntary and nonrandomized, residual confounding and selection bias cannot be excluded, and the findings should not be interpreted as establishing a causal effect of the app. REMEXDIS demonstrates the feasibility of integrating patient-directed digital support with physician-directed LDL-C alerts into routine care for patients at high and very high cardiovascular risk. Randomized or prospectively controlled studies are warranted to evaluate causal effects, long-term cardiovascular outcomes, cost-effectiveness, and the contributions of the individual components of the digital intervention.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/data11100250/s1. Figure S1: Representative screenshots of the REMEXDIS mobile application.

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https://doi.org/10.3390/data11100250

Funding: This study was funded by Amgen México, S.A. de C.V., through an unrestricted grant for an investigator-initiated project. Medicaweb, S.A. de C.V., as a Contract Research Organization, provided limited operational and methodological support for study monitoring and quality control. The Mexican Social Security Institute Foundation oversaw financial administration and resource management. Amgen México, S.A de C.V., did not have access to the clinical data and did not participate in the study design, data analysis, interpretation of results, or preparation of the manuscript. Grant number 20217219.

Institutional Review Board Statement: The application is registered in the Public Copyright Registry in Mexico (application no. 03-2023-071909542800-01). The commercial notice "United for the Reduction of Cardiovascular Risk in Mexico" is registered under number 135294, and the trademark "REMEXDIS" is currently pending registration with the Mexican Institute of Industrial Property (file number 3198028).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data supporting the findings of this study are not publicly available due to patient confidentiality and ethical restrictions. De-identified data may be made available from the corresponding author upon reasonable request and subject to approval by the relevant institutional and ethics committees.

Acknowledgments: The authors would like to thank all the investigators and patients who agreed to participate in the REMEXDIS-IMSS Study**.** During the preparation of this work the author(s) used Web of Science Research Assistant in order to conduct their literature search. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Conflicts of Interest: All authors completed the ICMJE disclosure form. The authors declare no personal financial conflicts of interest related to this work. The institutional unrestricted grant from Amgen México, S.A. de C.V., and the operational role of Medicaweb, S.A. de C.V., are disclosed in the Funding statement; Amgen México, S.A. de C.V., had no access to clinical data and had no role in study design, data analysis, interpretation of results, or manuscript preparation.

Appendix A

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