# Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: the txt2heart Colombia randomised controlled trial

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# Evaluation of the efficacy and safety of text messages targeting adherence to cardiovascular medications in secondary prevention: the txt2heart Colombia randomised controlled trial

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## *Abstract*

**Background:** Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the world. Prevalence is estimated at around 100 million patients worldwide. There is evidence that antiplatelet agents and antihypertensive medication reduce the risk of new vascular events in this population, but treatment adherence is very low.

**Objective:** We developed an intervention based on behavioral modification techniques delivered via mobile short message services (SMS) to increase the adherence to pharmacologic treatment on patients with prior history of ASCVD.

**Methods:** We conducted a randomized controlled clinical trial for patients with a prior diagnosis of cardiovascular event such as acute myocardial infarction, unstable angina, cerebrovascular disease or peripheral artery disease in one centre in Colombia. Patients randomized to the intervention arm were assigned to receive SMS daily for the first 4 weeks, five SMS on week 5: three SMS per week from week 6, and one SMS from 8th week until 52nd week. Patients in the control arm received a monthly SMS reminding them of the next study appointment, requesting information about changes in phone number, thanking them for participating in the study and reminding them of the importance of the study. Primary endpoint was change in Low Density Lipoprotein-Cholesterol (LDL-C) and the secondary endpoints were change in thromboxane B2 levels, heart rate, systolic and diastolic blood pressure. Medication adherence was measured with the Medication Adherence Report Scale (MARS 5), mortality

and new cardiac hospitalization were assessed at one year end point. A logistic regression analysis and bivariate testing was performed.

**Results:** Nine hundred and thirty patients were randomized, 805 (87%) completed follow up, and were analyzed for the primary endpoint. There was no difference between arms in change of LDL-C at 12 months (P=.41). or for any of the secondary outcomes. No adverse events were reported.

**Conclusions:** In our study we did not find evidence that a behavior modification intervention delivered by SMS improved LDL-C, blood pressure levels or adherence at 12 months. More research is needed to evaluate whether different SMS strategies including personalized messages and with different timing are effective; future studies should include mixed methods to understand better why, for whom and in which context (e.g. health system, social environment) SMS interventions work (or not) to improve adherence in patients with ASCVD. Clinical Trial: Clinicaltrial.gov NCT03098186. Date of registration: March 31st 2017

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*Title*

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Abstract

Background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the world. Prevalence is estimated at around 100 million patients worldwide. There is evidence that antiplatelet agents and antihypertensive medication reduce the risk of new vascular events in this population, but treatment adherence is very low. An intervention was developed based on behavioral modification techniques delivered via mobile short message services (SMS) to increase the adherence to pharmacologic treatment on patients with prior history of ASCVD.

Objective

The main aim was to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD.

Methods

A randomized controlled clinical trial for patients with a prior diagnosis of cardiovascular event such as acute myocardial infarction, unstable angina, cerebrovascular disease or peripheral artery disease in one centre in Colombia. Patients randomized to the intervention arm were assigned to receive SMS daily for the first 4 weeks, five SMS on week 5: three SMS per week from week 6, and one SMS from 8$^{th}$ week until 52nd week. Patients in the control arm received a monthly SMS reminding them of the next study appointment, requesting information about changes in phone number, thanking them for participating in the study and reminding them of the importance of the study. Primary endpoint was the change in Low Density Lipoprotein-Cholesterol (LDL-C) and the secondary endpoints were the change in thromboxane B2 levels, heart rate, systolic and diastolic blood pressure, medication adherence, cardiac and non-cardiac mortality and hospitalization. Linear regression analyses and bivariate testing were performed.

Results

Nine hundred and thirty patients were randomized, 805 (87%) completed follow-up, and were analyzed for the primary endpoint. There was no evidence that the intervention changed the primary outcome LDL (*P*=.41), or any of the secondary outcomes evaluated (all p-value > .05). There was no evidence that the intervention was associated with adverse events.

*Conclusions*

In this study there was no evidence that a behavior modification intervention delivered by SMS improved LDL-C, blood pressure levels or adherence at 12 months. More research is needed to evaluate whether different SMS strategies including personalized messages and with different timing are effective; future studies should include mixed methods to understand better why, for whom and in which context (e.g. health system, social environment) SMS interventions work (or not) to improve adherence in patients with ASCVD.

Trial registration

Clinicaltrial.gov NCT03098186. Date of registration: March 31st 2017

Keywords: Randomized controlled trial, Colombia, Text Messaging, Cardiovascular Disease, Secondary Prevention.

## Background

Cardiovascular diseases are the leading cause of mortality in the world. Worldwide an estimated 17.5 million people died from cardiovascular diseases in 2017. Atherosclerotic cardiovascular disease (ASCVD) was responsible for 7.3 million deaths in 2007, the death toll increased to 8.93 million by 2017, during the same time period mortality associated with cerebrovascular disease increased from 5.29 to 6.17 million events. Moreover 82 % of deaths in people younger than 70 years of age, took place in low and medium income countries [1].

In 2015 it was estimated that more than 100 million people worldwide had a diagnosis of ASCVD [2]. This population has been estimated to be at four to five times greater risk of a new cardiovascular event in comparison with individuals without a previous ASCVD [3].

Robust evidence indicates that the use of antiplatelet agents, beta blocker agents, ACE inhibitors and statins reduce the incidence of future fatal and non-fatal cardiovascular events in this population, and it is cost effective. These medications are recommended in all international guidelines for the management of people with ASCVD [4,5].

However, long term adherence to medication regime continues to be suboptimal, and many patients stop medication for reasons other than adverse side effects [6,7]. Less than half of patients with known ASCVD disease in high-income countries are receiving this group of cardiovascular medications, and the situation is much worse in Low-to-middle-Income Country (LMICs), where only 1 in 20 patients with ASCVD received all four types of cardiovascular drugs in 2011 [8].

The widespread use of mobile devices allows implementation of strategies such as text messaging to increase medication adherence. It has shown some promising results for people with diabetes [9], HIV [10] and tuberculosis [11] and therefore may help improve adherence for people with ASCVD [12,13]. In addition, access to the use of mobile telephones in the world has increased in recent years, an example of this is Colombia, whose telephone coverage went from 84% during 2009 to 98.1% for 2019 [14].

A 2017 Cochrane review evaluated the effects of SMS on adherence to medications in patients with ASCVD. The review identified seven trials (1310 participants) and showed a beneficial effect of SMS on adherence to medications in six of these trials. However, the quality of the evidence was very low. The Cochrane review identified the following limitations: (I) trials of small sample size (34 to 521 participants); (II) most trials had a short follow-up (<6 months); (III) primary outcomes reported were of limited clinical relevance; (IV) most studies recruited only patients with acute coronary syndrome, which leaves out an important group of patients with other arterial occlusive events (e.g., stroke, peripheral vascular disease and programmed coronary revascularization) who should be amenable for this type of intervention; (V) few studies were performed in LMICs and (VI) most trials did not describe the processes behind the SMS content generation, and the few trials that did report these processes did not target the key knowledge and attitudinal factors that are known to influence adherence to medication; instead, the interventions were simple ‘reminders’ [15]. In summary, although there are some promising small studies, there is a need to provide high-quality evidence to assess the effect of SMS interventions based on behaviour-change techniques to increase long term adherence to medications in patients with ASCVD in LMIC.

This study aimed to fill in this gap, and provides evidence whether theory based, and context specific text messages increase medication adherence in the secondary prevention of individuals with ASCVD in Colombia. We developed an intervention (text message) following the recommendations of Abroms *et al* including: a review of the literature, conduct of qualitative studies, and use of formal

theories and behavioural change techniques (Transtheoretical Model of Behaviour Change). Further details of our intervention development have been described previously [16,17].

The main aim of this study was to evaluate the efficacy and safety of an intervention with SMS messages delivered by mobile phones to improve adherence to cardiovascular medications in patients with ASCVD. The intervention efficacy was assessed via the measurement of blood serum low-density lipoprotein cholesterol (LDL-C) levels as an indicator of adherence to statins, systolic blood pressure as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs) and heart rate as an indication of adherence to beta-blockers. The secondary objectives were to assess the impact of mobile text messaging on self-reported adherence to medications, hospitalisations and the composite endpoint of incident major adverse cardiovascular events at 12 months.

## Methods

The full methodology of TxT2Heart Colombia has been previously published[15] and is summarized here. We report the study following the CONSORT recommendations [18].

### Study design

Two-parallel arm, single-blind individually randomised controlled trial.

### Participants

Adult patient's ≥18 years old with a history of at least one of the following arterial occlusive events were included: acute coronary syndrome (unstable angina, acute myocardial infarction with or without ST elevation), stable angina, ischaemic cerebrovascular disease, peripheral arterial disease or coronary revascularisation (coronary artery bypass surgery or percutaneous transluminal coronary angioplasty). Patients had to own a mobile phone and be able to read SMS. Patients were excluded if they had a known contraindication to take all the appropriate cardiovascular secondary prevention medications. All patients attended a single center, the Fundación Cardiovascular de Colombia (FCV), a tertiary hospital serving as a reference center for cardiovascular diseases in Northeastern Colombia. The hospital has a clinical studies office and has been certified in good clinical practice by national

and international authorities. All electronic health records were scanned using Structured Query Language (SQL) queries, looking for patients with no less than one month and without a maximum limit of time elapse since the last hospitalization for ASCVD. Records were then manually inspected by 2 experienced medical doctors. Qualifying patients were contacted by phone, and if they met the study´s inclusion criteria, were currently admitted or attended the outpatient clinic with an ASCVD diagnosed, were invited to participate. The process for evaluating potential eligible individuals is described in appendix 1. Written informed consent was obtained from all subjects prior to study activities.

Intervention

The intervention consisted of Behavior Modification Techniques (BCT) based on the Transtheoretical Model (TTM) [19] to be delivered via SMS. In a previous study designed by the same staff of the present study, a protocol was carried out to determine the content, quantity and frequency of sending SMS through focus groups, validation of experts, user feedback and pretest [17]. The messages included information on the health implications of adherence to health habits (or lack thereof). They included information on indications and recommendations on how to take their medication, to promote healthy medication habits, and provided or encouraged social support activities for the correct compliance with the prescribed treatment. The result of that study was 86 msm (including 12 msm of control and one welcome to the study) these were the messages used as an intervention in this clinical trial as well as the methodology of its delivery.

The SMS were sent through an automated text messaging platform (telerivet), which was fed directly with data registered in Commcare, which was the platform for registering patients. Volunteers were informed about the unidirectional nature of the test messages and warned that no replies were expected. If the patients wrote the word “PARE” or “Detener” (stop in Spanish), then no more messages were delivered. Text messaging started a day after patient randomization. Messages were

delivered every day for the first 4 weeks and then five messages were delivered in the 5th week. From the 6th week on, three messages were delivered per week and then beginning from the 8th week till the 52nd week, one message was delivered per week. Messages were delivered on random weekdays from 8:00 to 18:00 hours in order to prevent patients from predicting delivery times, in accordance with a previous validation with study subjects. If the patient withdrew from the study, or died SMS stopped. No Tailoring considerations or modifications were made during the trial.

Control

Patients in the control group only received text regarding the next study appointment, requesting information about changes in phone number, thanking them for participating in the study and reminding them of the importance of the study. Messages were sent every month. These messages were also sent to the intervention group and were generated during the text message validation on the general population.

Examples of Txt2Heart Colombia SMS messages are included in appendix 2.

Outcomes

The primary outcome was change in plasma LDL-C levels, at 12 months. Blood samples were obtained at the inclusion visit and at the end of the study appointment. Improvement in LDL cholesterol was considered a surrogate indicator of adherence to statin treatment. The secondary outcomes were systolic blood pressure as an indicator of adherence to blood-lowering therapies (ACE inhibitors or ARBs), heart rate as an indicator of adherence to beta-blockers, urine levels of 11-dehydrothromboxaneB2 adjusted for creatinine as an indicator of adherence to antiplatelet therapy; self-reported adherence to cardiovascular medications used in secondary prevention as measured using the Medication Adherence Report Scale-5 (MARS-5) questionnaire and rates of cardiovascular death or hospitalisation due to cardiovascular disease and non-cardiovascular death or hospitalisations due to non-cardiovascular disease. We also included road traffic crashes (the only

potential known hazard of text messaging) and death due to all causes as secondary outcomes.

The psychometric properties of the MARS-5 scale have been reported [20]. The MARS-5 demonstrated acceptable reliability (internal and test-retest) and validity (criterion-related and construct validity). Internal reliability (Cronbach's $\alpha$) ranged from 0.67 to 0.89 across all patient groups; test-retest reliability (Pearson's r) was 0.97 in Hypertension. Criterion-related validity was established with more adherent hypertension patients showing better blood-pressure control ($\chi 2=4.24$, df=1, $p<0.05$). Construct validity with beliefs about medicines was demonstrated with higher adherence associated with stronger beliefs in treatment necessity, and lower concerns about the medication.

All study participants were seen twice, on admission to the study, for baseline assessment and randomization, and at the end of follow-up period at a 12-month office visit. A follow-up telephone call was made three months after the randomization asking about new hospital admissions, all cause death or cardiovascular death, adverse events were also recorded. Systolic blood pressure, resting heart rate and urinary levels of thromboxane B2, were registered at the first and final visits. Self-informed cardiovascular medication prescription compliance was assessed with the MARS-5 at both visits. The scale was applied by trained personnel, considering automatic compliance if a total score of 25 was achieved. The subjective medication intake compliance was assessed on the previous 7 and 30 days. Data obtained about recurrent ASCVD was requested on the phone interview or by physical examination, oral reports by patient or relatives was allowed, and cardiovascular or any cause mortality was recorded. Information obtained on the phone was confirmed in all cases by reviewing medical case notes, registries or death certificates. Written evidence for any event was requested via electronic mail, Whatsapp messaging or case notes copies. If death or any major event or hospital admission occurred during the follow-up period, a hard copy of death certificate at the patients' relatives or case notes was requested on the 12-month follow-up visit. On the final follow-up all biomarkers were processed at the same time to avoid interference of difference in the reactive

processing and following the simple handling protocol depicted on annex 2. At the initial appointment we recorded at least three different phone numbers and a complete house address for each subject. A study identification card was provided with a written record of the date of the last visit to the trial, name of the Principal Investigator and clinic contact phone numbers. To ensure no loss of follow-up, any home number modification was actively searched and recorded. The appointment follow-up interval was kept such as to avoid any interference with study results.

Sample size

The original sample size of the study was 1600 participants, based on having 97% power to detect a 10% difference between arms in adherence. In the published protocol of this trial [16] a table with power calculations under different scenarios of assumptions was included. However, due to limited study funding the final sample recruited was 930 participants with 805 reporting LDL in the final visit. With 400 patients per arm (based on an expected mean reduction of 80 mg/dl on plasma levels of LDL-C in an adherence population and an expected mean reduction of 16 mg/dl on a non-adherent population to Atorvastatin 20mg), and assuming a 5% type-I error, a power of over 92% was estimated to detect a 10% difference in protocol compliance between both intervention arms. A table with power calculations for this sample size under different assumptions has been included in the appendix 3.

Randomization

A block randomization was used, with block sizes of 5 patients each, with a 1:1 allocation, assignment was done automatically using a remote computer-based randomization. Once the patient met the inclusion and exclusion criteria, and signed the consent form, the data capture platform (Commcare) applied a logarithm of randomization assigning the arm for the patient. This information was not shown to the interviewer to maintain blindness, but he did have confirmation of its effective completion on the digital form. The data capture platform accessed the services of the SMS sending platform (Telerivet), categorizing the group of SMS to send according to the assigned group.

Blinding

Due to the nature of the intervention, participants could not be blinded. However, all investigation personnel inputting data were blinded to the individual´s group assignment and all patients were told not to reveal their allocation details to study personnel. The study had an Engineer who was the only person who could access the messaging and database platforms. He could access the data in order to sort patient queries or help solve reception or technical issues. He was specifically trained on the importance of maintaining blinding. Investigators handling and analyzing data were all blinded to the intervention assigned.

Statistical analysis

The distributions of the baseline characteristics were compared between the intervention and control groups for all the randomized patients, those who completed the follow-up and those who did not complete the follow-up, performing an intention-to-treat analysis. Analysis of the continuous outcomes, (LDL-C, Thromboxane, heart rate, systolic and diastolic blood pressure, and quantitative measures of adherence) was performed using linear regression models. In each model the dependent variable is the difference between 12 months follow-up and baseline of the outcome, and the main explanatory variable is the intervention group. Furthermore, the Patient Health Questionnaire (PHQ9) scale (to measure depression) was collected at baseline as it was considered a potential confounding factor for adherence to medication. All linear regression models were adjusted by the baseline value of the outcome centred on the mean. The effect of the intervention is the difference, between arms, in the expected change of an individual with an average outcome value at baseline. Binary outcomes (hospitalisation and mortality) were analysed comparing the proportion of occurrence in both arms. No adverse events were reported so we did not conduct any analyses regarding this outcome. All p values were from 2-sided tests, the data was analysed using STATA version 14.0. No interim analysis was performed.

## Ethical considerations

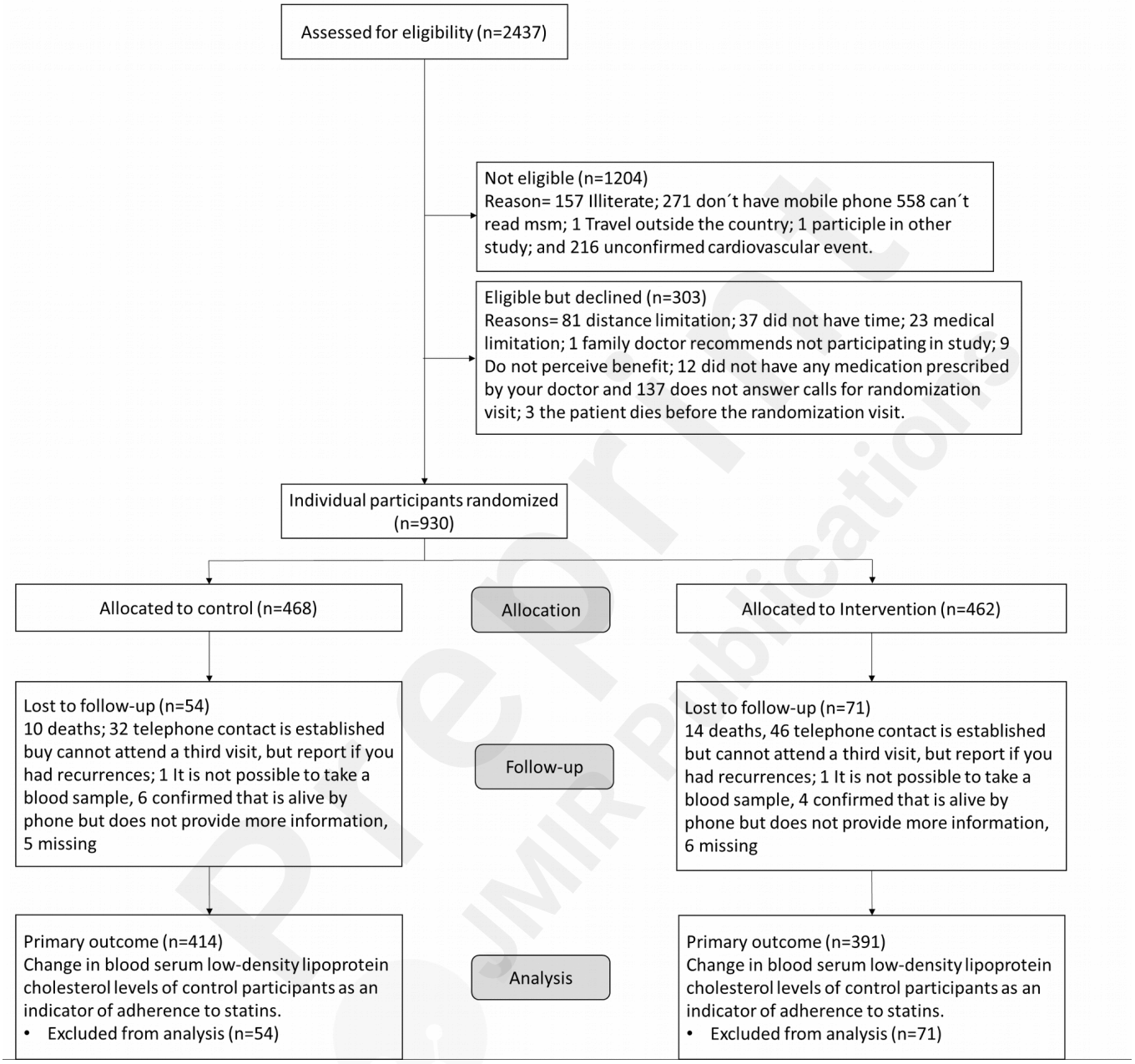
The Ethics Committee of Fundación Cardiovascular de Colombia evaluated and approved the trial (reference 375-2015). The study was conducted in compliance with the protocol, regulatory requirements, Good Clinical Practice and ethical principles of the Declaration of Helsinki, and the clinical investigations guidelines of the Fundación Cardiovascular de Colombia.

Data Availability Statement: The data generated during this study are not public because availability was not included in the study plan approved by the ethics committee and in the informed consent obtained from the participants. However, the data are available from the corresponding author on reasonable request.

## Results

Participants flow: Between April 18, 2017, and August 21, 2018, 930 patients were randomized. 462 were assigned to the intervention arm, and 468 were included in the control arm (Fig. 1). 16 patients texted “stop” to the messages (6 in intervention group and 10 control), all of them were followed up until the end of the study. In total, 125 losses to follow-up occurred, 71 in the intervention group and 54 in the control group.

Figure 1. CONSORT diagram.




Eight hundred five (87%) participants completed the trial follow-up at 12 months for the primary outcome (intervention group, n = 391; controls, n = 414) (Fig. 1). Retention did not differ between arms (15.2% in the intervention group versus 11.3% in the controls, $P$ = .09). The main predictors of retention were male gender (OR: 1.61 95% CI 1.05-2.46, $P$ = .03) and high total PHQ9 score (OR: 0.37, 95% CI 0.15-0.92, $P$ = .03). The effect of these predictors did not differ by group (interaction test values with $P$ > .05). The characteristics of the participants that completed the follow-up and

those who did not are reported in the additional file Annex 1. Eight hundred and five patients were evaluated for secondary outcomes HR, SBP, and DBP. Eight hundred and one patients were evaluated for TxBA2 because four patients were unable to deliver the urine sample. Eight hundred and seven patients were assessed with the MARCH 5 scale. New cardiovascular events were evaluated in 910 patients and mortality in 919 through telephone interviews.

Baseline characteristics: The baseline characteristics of the participants, which were similar between the two groups, are summarized in Table 1. 78.39% were men and the mean age was 63.52 years. 88.92% of the patients were using statins, while 94.52% were in anti-platelet aggregation therapy; moreover, beta-blockers use was reported in 83.23% participants while ACEi or ARBs use was observed in 68.06%. The average MARS score at baseline was 22.8, with about 40% considered adherent (MARS score=25). Clinical and laboratory characteristics such as PHQ9, BMI, LDL, SBP, DBP, HR, and TBX2 were similar between the two groups (Table 1). The baseline characteristics in participants with primary outcome completers and primary outcome non-completers are shown in the appendix 4 and the MARS 5 score at baseline in the appendix 5.

**Table 1. Characteristics of all participants at baseline**

| Characteristics | Control N= 468 | Intervention N=462 | All participants N=930 |
|---|---|---|---|
| Age, mean [SD] | 63.1 [10.0] | 64.0 [9.7] | 63.5 [9.8] |
| Gender, female, n(%) | 92 (19.7) | 109 (23.6) | 201 (21.6) |
| **Time since the last event, months, n (%)** | | | |
| Less than 3 months | 62 (13.3) | 43 (9.3) | 105 (11.3) |
| 3 to 12 months | 84 (18.0) | 97 (21.0) | 181 (19.5) |
| 1 to 3 years | 144 (30.8) | 122 (26.4) | 266 (28.6) |
| More than 3 years | 178 (38.0) | 200 (43.3) | 378 (40.7) |
| **Type event, n (%)** | | | |
| Acute coronary syndrome | 336 (71.8) | 327 (70.8) | 663 (71.3) |
| Stable angina | 33 (7.1) | 23 (5.0) | 56 (6.0) |
| Ischaemic Cerebrovascular disease | 21 (4.5) | 21 (4.6) | 42 (4.5) |
| Peripheral arterial disease | 15 (3.2) | 21 (4.6) | 36 (3.9) |
| Coronary revascularization | 63 (13.5) | 70 (15.2) | 133 (14.3) |
| **Prescribed with, n (%)** | | | |
| Statins | 414 (88.5) | 413 (89.4) | 827 (88.9) |
| ACEi or ARBs | 327 (69.9) | 306 (66.2) | 633 (68.1) |
| BB | 382 (81.6) | 392 (84.9) | 774 (83.2) |
| Platelet aggregation inhibitors | 442 (94.4) | 437 (94.6) | 879 (94.5) |
| MARS, mean [SD] | 22.8 [3.78] | 23.0 [3.31] | 22.9 [3.6] |
| Adherent (MARS=25 points), n (%) | 199 (42.5) | 189 (41.0) | 388 (41.7) |
| Self-reported adherence, last 7 days, (0-10 scale), mean [SD] | 9.1 [2.04] | 9.1 [2.19] | 9.1 [2.1] |
| Self-reported adherence, 30 days, (0-10 scale) , mean [SD | 9.1 [1.95] | 9.1 [2.05] | 9.1 [2.0] |
| **PHQ9, n (%)** | | | |
| Minimal depression (<5) | 343 (73.3) | 323 (69.9) | 666 (71.6) |
| Moderate depression (5-14) | 112 (24.0) | 127 (27.5) | 239 (25.7) |
| Moderately severe depression or severe (>14) | 12 (2.6) | 13 (2.8) | 25 (2.7) |
| **Smoking, n (%)** | | | |
| You are Smoker | 16 (3.4) | 12 (2.6) | 28 (3.0) |
| Never smoked | 168 (35.9) | 185 (40.0) | 353 (38.0) |
| You were a smoker | 284 (60.7) | 265 (57.4) | 549 (59.0) |
| Body mass index (BMI), mean [SD] | 27.9 [4.2] | 27.3 [4.2] | 27.6 [4.2] |
| Low density lipoprotein (LDL), mean [SD] | 88.2 [37.4] | 88.5 [38.0] | 88.4 [37.7] |
| Systolic blood pressure (SBP), mean [SD] | 128.2 [20.8] | 129.9 [20.9] | 129.0 [20.9] |
| Diastolic blood pressure (DBP), mean [SD] | 71.5 [11.7] | 71.9 [11.3] | 71.7 [11.5] |
| Heart rate (HR), mean [SD] | 68.9 [11.7] | 68.8 [10.6] | 68.8 [11.1] |
| Thromboxane B2 (TBX2), mean [SD] | 64.1 [147.2] | 64.2 [167.7] | 64.2 [157.6] |

## Outcomes

We did not find evidence ($P$ = .41) that the intervention was more effective than the control in

changing plasma LDL-C levels (adjusting by baseline value) at 12 months. We also did not find evidence between the two groups for any of the secondary outcomes including thromboxane B2 levels, heart rate, systolic blood pressure, diastolic blood pressure, adherence measured by MARS 5, or clinical events (hospitalization or death) at one year of follow-up (table 2).

**Table 2. Summary of primary and secondary outcomes**

| | Baseline | | Difference (Final – baseline) | | Difference adjusted by baseline | | |
|---|---|---|---|---|---|---|---|
| | Control | Intervention | Control | Intervention | Coef | *p* | IC |
| LDL | 88.0 [36.9] | 88.0 [37.5] | 5.1 [31.8] | 7.0 [33.8] | 1.85 | .42 | (-2.5, 6.2) |
| Thromboxane B2 | 61.2 [133.2] | 58.8 [138.1] | -19.6 [131.0] | -18.6 [94.0] | -0.28 | .96 | (-10.54, 10.0) |
| HR | 68.6 [11.6] | 68.5 [10.5] | -0.1 [13.9] | 0.6 [10.5] | 0.54 | .48 | (-1.0, 2.1) |
| SBP | 128.0 [21.2] | 129.3 [20.6] | 1.3 [19.4] | 0.8 [20.7] | 0.14 | .91 | (-2.3, 2.6) |
| DBP | 71.5 [11.9] | 71.7 [11.3] | 0.7 [11.7] | -0.1 [10.7] | -0.70 | .30 | (-2.0, 0.6) |
| MARS-5 | 22.8 [3. 8] | 23.1 [3.1] | 0.2 [3.7] | -0.02 [3.4] | -0.01 | .96 | (-0.4, 0.4) |
| Self-reported adherence (7 days) | 9.1 [2.1] | 9.2 [2.0] | 0.1 [2.0] | 0.2 [2.0] | 0.05 | .69 | (-0.2, 0.3) |
| Self-reported adherence (30 days) | 9.1 [2.0] | 9.2 [1.9] | 0.1 [1.9] | 0.1 [2.0] | 0.02 | .83 | (-0.2, 0.2) |
| Change in adherence (odds of worsen/improve) (1) | | | 1.2 (0.2) | 1.1 (0.20) | 0.94[a] | .81 | (0.6, 1.5) |
| Hospitalization for cardiovascular events (2) | | | 7.0% (32) | 6.0% (27) | 0.85[b] | .54 | (0.5, 1.4) |
| Hospitalization for any cause (2) | | | 10.7% (49) | 11.1% (50) | 1.03 | .92 | (0.71; 1.5) |
| Death to cardiovascular events (2) | | | 0.7% (3) | 0.4% (2) | 0.68[b] | 1.00 | (0.1, 4.0) |
| Death from any cause(2) | | | 1.7% (8) | 3.1% (14) | 1.77 | .20 | (0.8; 4.2) |

(1) within each group is the number of patients that lose adherence over those that turn adherent, (a) Odds Ratio

(2) within each group is the proportion of patients with event (b) Risk Ratio

Sample sizes may vary slightly because some individuals have missing values.

There were no adverse events related to the study. In total, three falls that required hospitalization were reported; in all of them, medical evaluation and a patient interview were performed, discarding any relationship of the mobile phone use and the fall events. There were no traffic accidents.

## Discussion

This study, a behavioral modification intervention delivered by SMS did not decrease LDL-C, the primary outcome, has not found evidence of an impact on any of the other biological markers assessed including blood pressure, heart rate or thromboxane, clinical events or on medication adherence as measured by the MARS-5 or self-reporting.

This study has many strengths; it has followed a thorough and detailed formative research to develop a tailored behavioral modification intervention, which has been previously published alongside the study protocol [16]. Different outcomes has been collected including self-reporting of adherence, validated adherence tools (the MARS-5 has demonstrated acceptable reliability (internal and test-retest) and validity (criterion-related and construct validity)[20]. and proxy biological markers and they were triangulated to evaluate adherence. A rigorous plan was put in place to ensure the intervention was delivered appropriately, study investigators collecting data were blinded to the patient allocation arm, and we followed up most patients for the primary and secondary outcomes at 12 months. Finally, even if the sample size was smaller than originally planned, still, to the best of our knowledge, this study is the largest so far to assess the effect of a behavioral modification intervention delivered by SMS to increase adherence in people with ASCVD.

This study also presented some limitations; although text sending could be confirm, the correct reading of the message could not evaluate, nor it was evaluated which stage of the transtheoretical behavioral modification was reached by each participant [17]. Also, inability to blind patients would have increased the likelihood of under-reporting nonadherence. This is a common problem with self-reports when patients may exaggerate their adherence if they believe that reports of non-

adherence will disappoint their health provider (self-presentational bias) [21]. The MARS addresses this problem by taking steps to diminish self-presentational bias. Introductory statements normalise nonadherence conveying a 'no-blame' approach [8]. In an additional step to minimise self-presentational bias, patients were told that their responses to the study questionnaires would not be seen by the healthcare professional providing their care. Also, we conducted a complete case analysis assuming missing not at random, but because of the low rate of loss to follow up and that its main predictors (sex and PHQ9) were similar in both arms we would not expect this to have a major impact on the trials results.

Another limitation was that SMS messages was not customize according to patients' categories. However, as mentioned above, this formative research was detailed, and a formal theory was applied to develop the content of the messages. Unfortunately, due to lack of funding, we could not conduct a comprehensive mixed method process evaluation to shed light on some of the mechanisms and contexts that could explain the effect on specific subgroups of patients. Finally, measuring adherence is always challenging, validated scale (MARS-5) was used and self-reported measures but pill count not; however, the direct measurement of adherence was complemented with indirect measurement such as LDL-C, blood pressure, heart rate and thromboxane.

A previous Cochrane review published in 2017 has identified studies reporting positive effects but all with small sample sizes, high risk of bias and therefore a low level of evidence [22]. The TEXT ME study was a randomized controlled trial which included 710 patients with coronary artery disease which did not report medication adherence but did report that 4 text messages sent per week led to reductions in LDL-C and blood pressure at 6 months [23]; on the other hand a more recent multi-centre randomized control trial in China including 822 patients with coronary artery disease reported that SMS messages did not reduce blood pressure or LDL-C at six months [24].

The lack of evidence of a beneficial effect reported of the intervention could be due to different reasons; the study might have lacked the power to detect an effect as the sample size was lower than

intended, however, with 930 patients it was well powered to detect a reasonable, modest, clinical benefit. The lack of benefit could be potentially explained by the fact that the baseline levels of medication adherence were already quite high with mean MARS of 9.1/10 at 7 and 30 days and therefore there was small room for improvement. Another possible explanation could be related to the content of the intervention. Although the intervention went beyond simple prompts and reminders (a thorough process was followed with the objective to change beliefs and motivations) perhaps it was not tailored enough to change beliefs and motivations in the study context, or perhaps in this highly adherent population these issues were not the main drivers of non-adherence. The findings could also be related to issues related with the delivery of the SMS (timing, frequency, length of the intervention), due to the effects of fatigue, overload or loss of interest in MSM. SMS interventions have been shown to be effective to modify lifestyle issues (such as tobacco cessation) where the goal of the patient and the intervention are closely aligned but they might be less effective on adherence [25]. Additionally, another possible explanation is that the results were measured at 12 months and it has been shown that adherence interventions are more effective in the short term (3 to 6 months) [26]. Planning only one intermediate measure at 3 months to assess the presence of rehospitalizations or death may be limiting the comparison of this study with others, but the protocol prioritized the pragmatic conditions of the trial, avoiding face-to-face contacts (such as adherence questions), because this would represent an additional study activity to the real scenario of the patients, leading to a potential Hawthorne effect that can alter the results of the effectiveness of text messages. Also, another explanation for the difference found with the studies included in the Cochrane review could be related that only a third of patients recruited in our study had the index event within the last year.

Finally, having data from a single site is a limitation to generalize these results to different scenarios, however it is important to note that the institution where the study was carried out is a reference center in northeastern Colombia, and its area of influence included a population of 5 million.

In conclusion, this study did not find evidence that a behavior modification intervention delivered by

SMS improves medication adherence, LDL-C or blood pressure levels at 12 months. The potential use of SMS for increasing medication adherence in patients with ASCVD is still a potentially attractive and scalable solution to a very important problem but further research is needed. Future research should include interventions (including SMS blended with other components) tailored to the specific issues and beliefs of individual participants, and more implementation studies using mixed-methods and innovative approaches that evaluate how different intervention characteristics (behavioral modification component), SMS delivery strategies (timing of initiation, frequency, duration, and personalization) and context (type of patients, health system, social environment) influence the effect of this intervention.

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Author contributions

All authors Clinical protocol review, JC, PP, NS, AB, KC Logistics organization; AB, JC, PP, CF, AU, PP, RH, JS, FS, DCG, KC evaluation of the questionnaire; DP, AB statistical analysis; DP, AB, PP formal analysis and data presentation; DP, PP result validation; NS, PP, JC, AU fund acquisition; AB, DP, PP, JS original draft; PP, JC, CF, NS, AB, AU, EM, RH, LA, KM, AC conceptualization of the study; NS, EG Formulation, application and validation of biological samples. All authors wrote, reviewed and edited.

Competing Interests statement

The authors declare that the research was conducted in the absence of any commercial or financial

relationships that could be construed as a potential conflict of interest.

Appendix

Multimedia Appendix 1 [Evaluating potential eligible individuals]

Multimedia Appendix 2: [Example of the SMS intervention]

Multimedia Appendix 3. [Sample size calculations]

Multimedia Appendix 4: [Baseline characteristics in participants with primary outcome completers and primary outcome non-completers]

Multimedia Appendix 5: [Distribution of the MARS 5 score at baseline]

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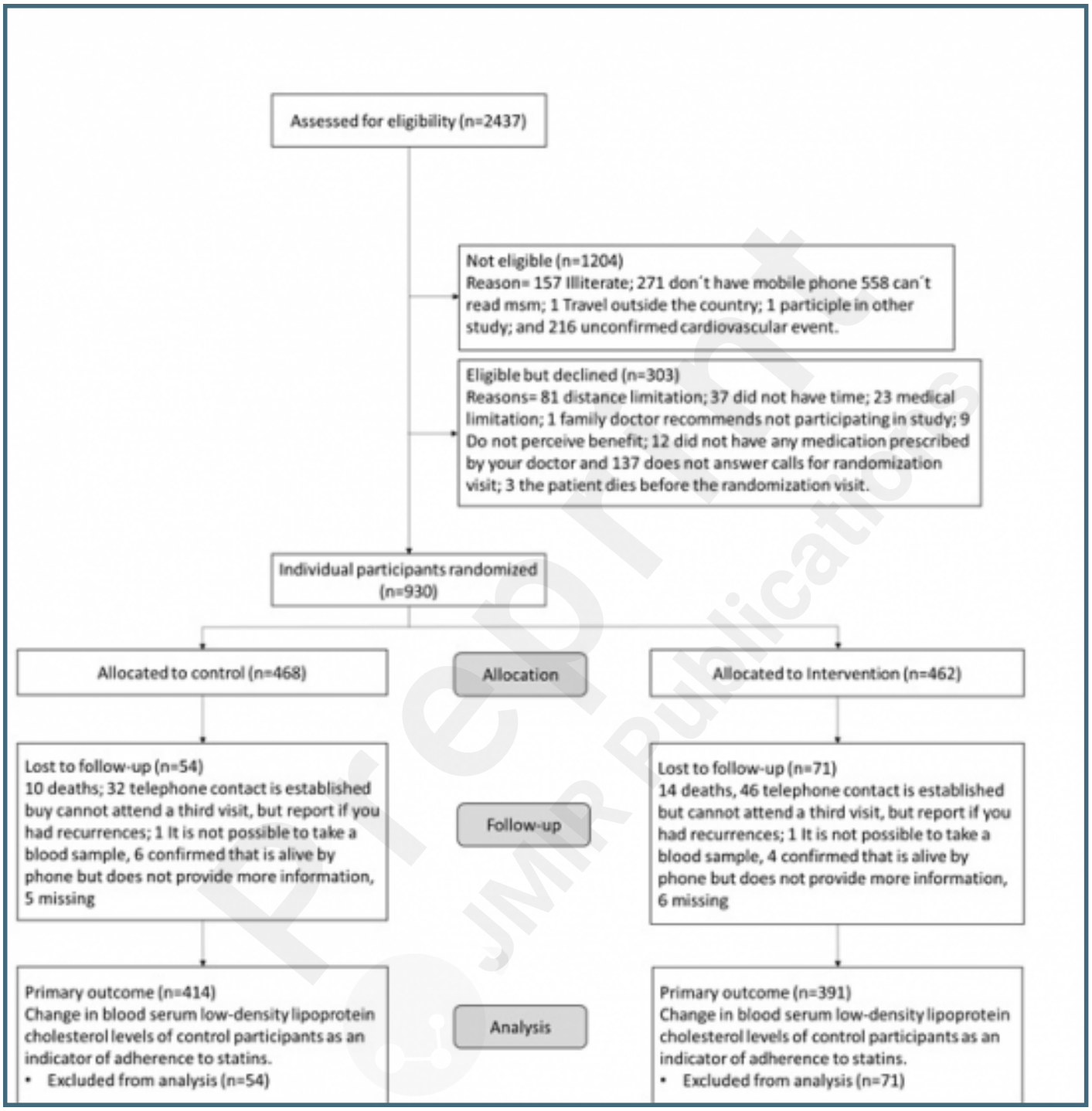
# Supplementary Files

# Figures

CONSORT diagram.



# Multimedia Appendixes

Evaluating potential eligible individuals.
URL: http://asset.jmir.pub/assets/1d62bd0d6391f942509341e1b7ab93cb.png

Example of the SMS intervention.
URL: http://asset.jmir.pub/assets/a14a9db173ca38ee6226015a3b1776fb.docx

Sample size calculations.
URL: http://asset.jmir.pub/assets/f56816b8ae1e705e19cfa09d780398e4.docx

Baseline characteristics in participants with primary outcome completers and primary outcome non-completers.
URL: http://asset.jmir.pub/assets/ad95354ec15e83ea18add6d9b2c2c4e1.docx

Distribution of the MARS 5 score at baseline.
URL: http://asset.jmir.pub/assets/9e07d888be49b9019de5a03dbce235a1.docx

# CONSORT (or other) checklists

CONSORT_Checklist.
URL: http://asset.jmir.pub/assets/ef36f51d79c03771a4609c64c6b33d5b.pdf

# Related publication(s) - for reviewers eyes onlies

The txt2heart Colombia randomised controlled trial protocol_ BMJ Open_Published.
URL: http://asset.jmir.pub/assets/97eaf3c12671a735f445161812d44c0c.pdf

Designing a text messaging program.
URL: http://asset.jmir.pub/assets/e204c2587ea886bd8ad226e0ca715912.pdf

Response letter reviewers_2.
URL: http://asset.jmir.pub/assets/b6702831fe17fd379b57a85187fa84cb.pdf