Long-lasting Control of LDL-Cholesterol Induces a Forty Percent Reduction in the Incidence of Cardiovascular Events:

New Insights from a 7-year Study

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Running Title: Controlled LDL Cholesterol reduces CV events

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ABSTRACT

Recent studies have yielded controversial results on the long-term effects of statins on the risk of cardiovascular (CV) events. In order to fill this knowledge gap, we assessed the relationship between LDL-C levels and CV events in hypertensive patients without previous CV events and naïve to antidyslipidemic treatment, within the “Campania Salute Network” in Southern Italy. We studied 725 hypertensive patients with a mean follow-up of 85.4±25.7 months. We stratified our population into 3 groups based on LDL-Cholesterol (LDL-C) levels in mg/dL: Group 1) patients showing during the follow-up a mean LDL-C value ≤100 mg/dL in absence of statin therapy; Group 2) statin-treated patients with LDL ≤100 mg/dL; Group 3) patients with LDL-C >100 mg/dL, with or without statins. No significant difference among the groups was observed in terms of demographic and clinical characteristics and medications. The incidence of first CV events was 6.0% in Group 1, 5.7% in Group 2 (n.s. vs Group 1), and 11.9% in Group 3 (p<0.05 vs Group 1 and Group 2). A stable long-term satisfactory control of LDL-C plasma concentration (≤100 mg/dL) reduced the incidence of major CV events from 1 event every 58.6 patient/year to 1 event every 115.9 patient/year. These findings were confirmed in a Cox regression analysis, adjusting for potential confounding factors. Taken together, our data demonstrate that a 7-year stable control of LDL-C induces a forty percent reduction in the incidence of CV events.

Key words: cardiovascular risk; cholesterol; dyslipidemia; hypercholesterolemia; hypertension; lipid-lowering therapies; MACE; statins.
Significance Statement (80 words maximum)

There are several discrepancies between Mendelian studies and other investigations on the actual effects of reduction of plasma concentration of LDL cholesterol on the incidence of major cardiovascular events. Taken together, our data in non-diabetic subjects show that a 7-year stable control of LDL cholesterol induces a ~40% reduction in the incidence of cardiovascular events.
NONSTANDARD ABBREVIATIONS

ACEi: Angiotensin Converting Enzyme inhibitors

ARB: angiotensin II type 1 receptor blockers

BP: Blood Pressure

bpm: beats per minute

CI: Confidence Interval

CV: CardioVascular

HDL-C: High-Density Lipoprotein Cholesterol

HR: Hazard Ratio

LDL-C: Low-Density Lipoprotein Cholesterol
Introduction

According to the analyses of the Cholesterol Treatment Trialists Collaboration, in clinical trials the control of low-density lipoprotein cholesterol (LDL-C) is accompanied by a fairly constant relative risk reduction in major cardiovascular (CV) events (~22-24% per mmol/L) after the first year, with no indication of increasing benefits when extending the treatment duration (Collins et al., 2016; Sabatine et al., 2018). Instead, Mendelian randomization studies have shown that each mmol/L reduction in LDL-C is associated with a 55% lower CV risk (Ference et al., 2012; Vincent, 2014). Such a difference may be attributable to the duration of exposure (Ofori-Asenso et al., 2018; Vani and Underberg, 2018; Ference et al., 2019), since in the Mendelian studies LDL-C differences are sustained over a lifetime. Interestingly, in 2022, Nelson Wang and collaborators (Wang et al., 2022) published a meta-analysis of randomized clinical trials, which were stratified by follow-up time and degree of LDL-C lowering, concluding that the results from short-term trials are compatible with the robust associations between LDL-C and CV events seen in Mendelian randomization studies inasmuch as the benefits of LDL-C lowering do not seem to be fixed but increase progressively with longer durations of treatment. However, as recognized by the Authors (Wang et al., 2022), their analysis was simply based on trial level data, while more reliable estimates would arise from the examination of individual data. Specifically, it should be noted that since the benefit of treatment mostly depends on the time during which the subject is exposed to a certain level of LDL-C, it becomes necessary to adopt as reliable controls those subjects who present LDL-C values within the range considered physiological throughout the entire follow-up period. Instead, in clinical trials, average values are usually reported with a more or less wide standard error, which implies that some subjects are really well controlled while others are not controlled at all. Using LDL-C data from individual patients is particularly important in light of the observation that in clinical trials the mean difference in plasma LDL-C concentration between the active treatment group and the placebo group decreases progressively during the follow-up period.
leading to an underestimation of the treatment benefit (Sacks et al., 1998; Cohen et al., 2000; Packard et al., 2021; Garcia-Fernandez-Bravo et al., 2022; Wang et al., 2022).

Moreover, data on the long-term effects of statin treatment are often the mere result of projections through statistical processing of those collected in shorter periods. For example, in Wang's meta-analysis (Wang et al., 2022), the proportional risk reduction at 40 years has been calculated based on data from 21 trials, of which 15 have a mean follow-up period of less than 5 years, and of the remaining 6, only two reach six years of observation.

In order to better understand these discrepancies, we have designed a study within the population of hypertensive subjects of the Campania Salute Network to specifically evaluate the effect of stable and long-lasting reduction of plasma LDL-C concentration on the incidence of major CV events in non-diabetic subjects with high CV risk but with negative medical history for CV events, with a follow-up period of at least 5 years.

Methods

Patients

We conducted a population-based retrospective cohort study using the Campania Salute Network, which is an open electronic registry of the Hypertension Research Center of the “Federico II” University Hospital in Naples (Italy), which also includes community hospital-based hypertension clinics and general practitioners from the Campania region (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02211365) (Mancusi et al., 2018; Canciello et al., 2021; Trimarco et al., 2022). Recruited subjects were referred to the Hypertension Research Center for clinical management and CV imaging (Ciccarelli et al., 2017). This dataset contains demographic data, information on diagnoses and therapies, and mortality-related reports (Izzo et al., 2017; Lonnebakken et al., 2017; Lembo et al., 2022). At the time of data extraction, the registry of the Campania Salute Network included data from more than 15000 patients. For the present analysis, hypertensive patients were selected when meeting the following inclusion criteria: age ≥18
years; no previous use of statins, at least 5-year follow-up. We excluded: 1) patients with conditions that could limit life expectancy (cancer, peripheral vascular disease, venous thrombosis, abdominal aortic aneurysm, and dementia; 2) subjects with coronary/cerebrovascular disease, diabetes mellitus, valvular heart disease, and atrial fibrillation; 3) patients with liver cirrhosis, which has been linked to non-trivial safety concerns that could discourage the use of statins. The follow-up time was defined as the time from enrollment until the end of follow-up, incident CV event or death, or loss to follow-up, whichever came first. The primary outcome of our study was a composite of incident CV events that included non-fatal events as non-fatal myocardial infarction or stroke, de novo angina, carotid stenting, myocardial revascularization, heart failure requiring hospitalization, transient ischemic attack, pulmonary embolism, or CV and non-CV death, as previously reported (Trimarco et al., 2022). The “Federico II” University Hospital Ethic Committee approved the database generation of the registry of the Campania Salute Network. All the subjects participating in the study signed an informed consent allowing the use of their data for scientific purposes.

**CV Risk Factor and Disease Assessment**

Data on demographics and risk factors were achieved at enrollment, including age, sex, race, history of myocardial infarction, diabetes, stroke, and smoking habit. The body mass index was calculated based on the values of body height and weight. As per current guidelines (Unger et al., 2020), systolic and diastolic blood pressure (BP) were measured after 5 minutes resting in the sitting position, three times at 1-minute intervals, as we previously described (Trimarco et al., 2022). Obesity was defined as a body mass index ≥30 kg/m². Fasting glucose was assessed by standard methods; diabetes was defined as history of diabetes, presence of a fasting blood glucose ≥126 mg/dL confirmed on at least 2 different occasions, or use of any antidiabetic medication (Mone et al., 2022). Lipid measurements on fasting blood samples were implemented at each study examination (Trimarco et al., 2022). Triglyceride and total cholesterol levels were measured
enzymatically, high-density lipoprotein cholesterol (HDL-C) was obtained after precipitation with dextran sulfate/magnesium chloride, and LDL-C was calculated applying the Friedewald equation, as we described (Trimarco et al., 2022). Estimation of creatinine clearance (estimated glomerular filtration rate) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

All data, including LDL-C concentrations, were collected at each visit (at least 2 visits/year); how often LDL-C was measured and the time between visits was not standardized (but followed the physician’s directions). Of note, all medical staff, including physicians, nurses, and pharmacists, asked patients about drug compliance and adverse reaction to confirm drug exposure and tolerability at each visit. The physician augmented the dosage of a statin or other prescribed co-medication(s) when LDL-C concentrations had not sufficiently decreased.

We stratified the study population into three groups based on LDL-C levels in mg/dL: 1) patients showing during the follow-up a mean LDL-C value ≤100 mg/dL in absence of statin therapy; 2) patients showing a mean value of LDL during the follow-up ≤100 mg/dL while treated with statins; 3) patients showing a mean LDL-C concentration during the follow-up >100 mg/dL with or without statins. From electronic medical records, we obtained all concomitant medication information (including daily dosage and duration), which were prescribed during the study periods in the “Federico II” outpatient Hypertension Center, by General Practitioners and Primary Physicians, or doctors in other hospitals within the Campania Salute Network.

**Statistical Analysis**

Data are shown as percentages for categorical variables and mean ± SD for continuous variables. ANOVA and χ² distribution were used for exploratory statistics. A Cox regression analysis was used to evaluate the effects of LDL-C on CV events during follow-up, adjusting for age and sex; patients with mean LDL-C level ≤100 mg/dL independently from statin therapy were used as reference for comparison. A 2-tailed p<0.05 was considered statistically significant.
Results

A total of 725 hypertensive patients met the study criteria. The mean follow-up was 85.4±25.7 months, so our population was monitored for 5162 person-years. As described in the Methods, we divided our population in 3 groups according to the LDL-C plasma levels: group 1 included 140 patients with baseline LDL-C ≤100 mg/dL who did not receive lipid lowering treatment and showed during the follow-up a mean LDL-C plasma concentration ≤100 mg/dL; patients of group 2 (N= 149) had baseline LDL-C plasma levels >100 mg/dL, received statin treatment and obtained a mean LDL-C plasma concentration during the follow-up ≤100 mg/dL; group 3 included 436 patients with baseline LDL-C >100 mg/dL who received a prescription of statins but failed to obtain a mean LDL-C plasma concentration ≤100 mg/dL during the follow-up. The baseline clinical and demographic characteristics of these 3 groups are reported in Table 1.

Our patients received one of the following statins alone or in combination with ezetimibe: atorvastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, and pravastatin, with the dosage adjusted during the follow-up if necessary, according to efficacy and tolerability. No significant difference among our groups was found in terms of antihypertensive medications (Table 2). We did not find any significant difference among groups in the total number of anti-hypertensive drugs: Controlled without statins: 3.48±0.6, Controlled with statins: 3.55±0.7, not-controlled: 3.44±0.6. We have added this info in the revised version of our manuscript.

The mean LDL-C plasma concentrations recorded during the whole follow-up period in the three study groups are depicted in Figure 1. A significant difference was detected between the values of Group 1 and Group 2 compared to the values recorded in Group 3.
In 5162 patient/years, 69 patients experienced their first CV event (including 26 coronary heart disease events, 4 coronary and 4 carotid revascularization, 15 strokes, 7 TIA, 10 congestive heart failure events, 2 CV deaths, and 1 non-CV death) with an incidence in patients treated with statins who obtained a mean plasma concentration of LDL-C ≤100 mg/dL during the whole follow-up (Group 2) comparable to that observed in hypertensive patients who did not require lipid lowering treatment on account of a LDL-C plasma concentration ≤100 mg/dL at baseline (Group 1) (6.0% vs 5.7%, n.s.). On the contrary, Group 3 displayed an incidence of major CV events of 11.9% which was significantly higher than the other two groups (p<0.05 for both groups).

A stable long-term satisfactory control of LDL-C plasma concentration (≤100 mg/dL) was able to reduce the incidence of major CV events from 1 event every 58.6 patient/years to 1 event every 115.9 patient/years, a value that is no longer different from that of normocholesterolemic hypertensives (1 event every 122.5 patient/years). With a total of 69 fatal and non-fatal CV events (9.4% of 725 participants), our population does not allow a separate analysis for each component of the composite endpoint because of a limited statistical power. We then performed a Cox regression analysis to assess the effects of LDL-C on CV events during follow-up, adjusting for age and sex, after merging subgroups with LDL controlled (with or without statins); thus, we demonstrated that the risk of CV events is significantly greater in uncontrolled patients with a HR of 1.953 (Table 3 and Figure 2).

Discussion

With the advent of electronic health records, longitudinal data are becoming progressively more and more available for accurate risk prediction in clinical practice, providing new openings to assess longitudinal data rather than utilizing single baseline measures (Califf and Platt, 2013). Indeed, data from clinical trials do not fully quantify the risk associated with LDL-C exposure
(Ference et al., 2019; Wang et al., 2022). Additionally, data examining long-term exposure to lower levels of LDL-C due to healthier lifestyle and/or genetic polymorphisms suggest that the LDL-C concentration over time is a critical determinant of CV risk (Cohen et al., 2006; Ference et al., 2012; Navar-Boggan et al., 2015; Domanski et al., 2020). The database of the Campania Salute Network, established in 1980, contains the clinical recordings of 15000 hypertensive patients (Trimarco et al., 2022); we decided to select hypertensives with a LDL-C plasma concentration >100 mg/dL, free of diabetes and CV events and statins naïve, with the availability of LDL-C data recorded at least every six months with a relatively long follow-up who responded favorably to statin therapy. This tool allowed us to explore the effects on CV risk of a long-term cumulative exposure to a normalized LDL-C level obtained by statins administration. Our control groups were: 1) hypertensives with similar demographic and clinical characteristics except a lifespan cumulative exposure to normal LDL-C plasma concentration as confirmed by the data obtained every six months during the follow-up; 2) hypertensive patients with similar demographic and clinical characteristics with a LDL-C plasma concentration >100 mg/dL who had a cumulative exposure to abnormally high LDL-C plasma concentration as demonstrated by the data obtained at six month interval during the long term follow-up. Valentin Fuster and co-workers indicated that the risk of CV events depends on the cumulative exposure to LDL-C (Domanski et al., 2020), which can be assessed by the area under the LDL-C curve. However, albeit mean LDL-C levels were relatively stable during this time, the individual patterns of LDL-C levels substantially vary from a decreasing trend (“negative slope” of LDL-C) to an increasing trend (“positive slope” of LDL-C). Therefore, we decided to evaluate cumulative LDL-C exposure through the mean of the values of LDL-C levels recorded at least every six months during the follow-up instead of the area under the curve of plasma LDL-C. We preliminary excluded diabetic patients in order to enroll only hypertensives at high CV risk so to assess the potentiality of statins in primary prevention. By using this approach, we were able to create 3 experimental groups: Group 1 with low exposure to LDL-C without anti-dyslipidemic treatment; Group 2 with low exposure to LDL-C only during the long-term follow-up
period on account of the favorable effect of statin treatment; Group 3 with high exposure to LDL-C due to the lack of effect of the prescribed statin therapy. The three groups showed similar demographic and clinical characteristics except for the sex distribution (lower percentage of women in group 1). The primary endpoint of our study was to define the effect of a stable reduction of LDL-C plasma concentration induced by a long-term statin treatment on the incidence of a composite of CV events. Our data demonstrate that a reduction below 100 mg/dl of plasma LDL-C level maintained for a mean follow-up period of 84 months is associated with a 40% lower CV risk. Even more interesting is the observation that seven years of statin therapy, by allowing a LDL-C plasma concentration in the physiological range, can completely abolish the excess of CV risk in patients with a baseline LDL-C plasma level >100 mg/dL. Evidence from a post hoc analysis of the Japanese REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease) trial, indicates that there is a threshold value of LDL-C (between 60 mg/dL for ischemic stroke and 80 mg/dL for CV death), below which further reduction does not seem to affect the onset of CV events in patients with coronary artery disease given statins for secondary prevention of CV disease (Sakuma et al., 2022).

To evaluate the time course of the reduction in the cumulative LDL-C exposure on the incidence of CV events during the follow-up, we merged the groups with controlled LDL (with or without statins: Groups 1 and 2) and performed a Cox regression analysis, adjusting for age and sex, since it has been reported that men with the same area under the LDL-C curve have a greater risk of subsequent incident CV events than women (Silverman et al., 2016; Domanski et al., 2020). This kind of analysis demonstrated that the two curves begin to diverge after one year of follow-up, then the difference in incidence of CV events progressively increases so that it is possible to calculate that after ~15 years the incidence in the high LDL-C group is 50% greater than in the other group, so that the HR ratio of developing a CV event is 1.953.
In a recent meta-analysis of randomized clinical trials designed to ascertain the time to benefit for prevention of a first major CV event, Lee and colleagues (Silverman et al., 2016) had suggested that in adults aged 50-75 years, 2.5 years are needed to avoid 1 major CV event for 100 patients treated with a statin, raising some doubts on the use of statins in primary prevention of CV events in adults aged 40 to 75 years who have a >7.5% risk of CV events within 10 years. On the contrary, our data support the conclusion that there is a primary prevention benefit to lower LDL-C, since a long-lasting reduction in LDL-C is able to reduce the rate of CV as much as expected from Mendelian studies (Ference et al., 2012).

The importance of cholesterol in predicting CV risk is of paramount significance (Razavi et al., 2023). While the detrimental role of LDL is relatively established (Abdullah et al., 2018), the protective role of HDL-C is being challenged; for instance, we have recently demonstrated that in hypertensive patients very high HDL-C levels are associated with higher incident CV risk (Trimarco et al., 2022). We also want to emphasize that circulating lipoprotein particles vary in size, density, and lipid/apolipoprotein composition and can be separated into several classes based on physical and chemical parameters. Specifically, the analysis of the circulating LDL profile can be carried out by several methods, including ultracentrifugation or gradient gel electrophoresis, in order to separate LDL particles based on their density or size (Ito et al., 2011; Ivanova et al., 2017). In this sense, small-density LDL-C (sdLDL-C) remains one of the most effective predictors of residual risk of future CV events in stable coronary artery disease patients using statins (Steinberg et al., 1989; Sakai et al., 2018). Even the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial confirmed the CV risk associated with sdLDL-C levels: in patients treated with rosuvastatin and with an average LDL-C of 54 mg/dL, a significant increase in CV risk was still associated with sdLDL-C (Mora et al., 2015). A recent study has confirmed that having sdLDL-C ≥50 mg/dL is a significant independent risk-enhancer of
atherosclerotic CV disease (Schaefer et al., 2023), most likely because these particles are more susceptible to chemical modifications (Orekhov et al., 1991) that may increase their atherogenicity.

The present study is not exempt from limitations. On account of the stringent inclusion criteria we were able to enroll 725 hypertensive patients and with a very long follow-up we reached more than 5000 patient/years but due to the demographic and clinical characteristics of the study population we recorded only 69 CV events, which do not allow a proper separate analysis of each component of the composite endpoint, mainly due to limited statistical power. Second, we are unable to explain why three out of four hypertensive patients who received a prescription of statins which should be reinforced every six months according to the lack of a satisfactory effect on LDL-C plasma level failed to obtain any reduction in mean LDL-C concentration during such a long follow-up. However this issue is not relevant for our conclusions, which are founded on the observation that, whatever the case, the lack of LDL-C satisfactory control is associated with higher rate of CV events. Intriguingly, the LDL-C difference between the treatment groups in randomized clinical trials diminishes during each additional year of follow-up, and this finding is generally attributed to non-adherence to randomized treatment (Silverman et al., 2016; Navarese et al., 2018; Wang et al., 2022). Furthermore, observational studies have reported that after six-month treatment ~50% of the patients in primary prevention had stopped the treatment and in the remaining 50% there is a very low compliance to the therapeutic prescription (Deambrosis et al., 2007; Mann et al., 2007; Perreault et al., 2009; Brown and Bussell, 2011). According to these observations, we can speculate that in our population these phenomena may account for the ambitious target of a LDL-C plasma concentration constantly ≤100 mg/dL for such a long follow-up. Third, we recognize that the results of meta-analyses should be confirmed by placebo-controlled randomized trials more than the results of retrospective observational studies.

A central strength of this study is the very long-term follow-up of hypertensive patients free of CV disease who had repeated measurements of LDL-C and other CV risk factors; our data from a
long-term cohort study provide a reliable estimate of the magnitude and the duration of LDL-C differences documented during many years of follow-up, showing that a pharmacological treatment that reduces plasma LDL-C below 100 mg/dL may help in the clinical management of primary prevention in hypertensive patients.
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AUTHOR CONTRIBUTIONS

Participated in research design: V.T., R.I., G.S., and B.T.

Performed research: P.G., M.V.M., I.F., and D.P.

Performed data analysis: R.I. and D.P.

Wrote or contributed to the writing of the manuscript: V.T., R.I., G.S., and B.T

Financial Disclosures

None.

Data Availability Statement

Reasonable requests to access the data used in these analyses can be made to the first Authors.
References


Table 1. Main characteristics of our population at baseline.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (N=140)</th>
<th>Group 2 (N=149)</th>
<th>Group 3 (N=436)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.4±12.4</td>
<td>67.9±10.3</td>
<td>66.3±10.5</td>
<td>0.121</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>51(36.4)</td>
<td>63(42.3)</td>
<td>224(51.4)</td>
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<tr>
<td>BMI, Kg/m²</td>
<td>28.8±4.4</td>
<td>28.7±4.5</td>
<td>28.1±4.3</td>
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<td>Fasting glucose, mg/dL</td>
<td>96.1±13.4</td>
<td>95.2±12.1</td>
<td>95.6±12.5</td>
<td>0.844</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>0.97±0.20</td>
<td>1.01±0.33</td>
<td>0.96±0.33</td>
<td>0.186</td>
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<tr>
<td>Total Cholesterol, mg/dL</td>
<td>174.1±31.8</td>
<td>203.7±34.2</td>
<td>216.7±34.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>LDL-Cholesterol, mg/dL</td>
<td>98.1±23.1</td>
<td>124.7±29.8</td>
<td>137.0±27.0</td>
<td>&lt;0.0001</td>
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<td>HDL-Cholesterol, mg/dL</td>
<td>47.4±11.7</td>
<td>51.3±14.3</td>
<td>50.1±12.3</td>
<td>0.105</td>
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<td>Triglycerides, mg/dL</td>
<td>130.7±81.6</td>
<td>138.6±68.8</td>
<td>138.8±74.0</td>
<td>0.373</td>
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<td>Serum potassium, mg/dL</td>
<td>4.2±0.5</td>
<td>4.4±0.5</td>
<td>4.3±0.5</td>
<td>0.226</td>
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<tr>
<td>Serum Uric acid, mg/dL</td>
<td>5.2±1.3</td>
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<td>5.7±4.7</td>
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<td>SBP, mmHg</td>
<td>145.1±16.6</td>
<td>149.2±23.0</td>
<td>148.2±21.7</td>
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<tr>
<td>DBP, mmHg</td>
<td>85.5±11.2</td>
<td>83.7±11.0</td>
<td>84.7±12.6</td>
<td>0.818</td>
</tr>
</tbody>
</table>

Values are mean±SD or number and percentage. ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; bpm: beats per minute; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure.
Table 2. Distribution of antihypertensive medications prescribed in at least 50% of visits, in the study population.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (N=140)</th>
<th>Group 2 (N=149)</th>
<th>Group 3 (N=436)</th>
<th>p</th>
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<tr>
<td>ACEi or ARB (%)</td>
<td>43.6</td>
<td>53.0</td>
<td>47.5</td>
<td>0.266</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>22.1</td>
<td>23.5</td>
<td>22.2</td>
<td>0.947</td>
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<tr>
<td>blockers (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>28.6</td>
<td>27.5</td>
<td>29.6</td>
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<td>β-blockers (%)</td>
<td>17.1</td>
<td>16.1</td>
<td>19.7</td>
<td>0.557</td>
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</table>

ACE: angiotensin-converting enzyme; ARB: angiotensin II type 1 receptor blockers.
Table 3. Cox regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Sign.</th>
<th>HR</th>
<th>95.0% CI</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
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<tr>
<td>Age</td>
<td>0.799</td>
<td>1.003</td>
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<tr>
<td>LDL-C uncontrolled vs controlled</td>
<td>0.016</td>
<td>1.953</td>
<td>1.136</td>
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<tr>
<td>Female sex</td>
<td>0.773</td>
<td>1.074</td>
<td>0.663</td>
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</table>
Figure Legends

Figure 1

Plasma levels of LDL-C recorded in the 3 study groups during the entire follow-up period.

Figure 2

Risk of CV events in patients with controlled or uncontrolled LDL-C.
Figure 1
Figure 2