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Authors

Santos, Raul D
Waters, David D
Tarasenko, Lisa
et al.

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A comparison of non-HDL and LDL cholesterol goal attainment in a large, multinational patient population: The Lipid Treatment Assessment Project 2

Raul D. Santos^{a,*}, David D. Waters^{b,1}, Lisa Tarasenko^{c,1}, Michael Messig^{c,1}, J. Wouter Jukema^{d,1}, Cheng-Wen Chiang^{e,1}, Jean Ferrieres^{f,1}, JoAnne M. Foody^{h,1}

^a The Lipid Clinic Heart Institute (InCor), University of São Paulo Hospital, São Paulo, Brazil

^b San Francisco General Hospital and University of California, San Francisco, CA, USA

^c Pfizer Inc., New York, NY, USA

^d Leiden University Medical Center, Leiden, The Netherlands

^e Cathay General Hospital and Taipei Medical University, Taipei, Taiwan

^f Rangueil Hospital, Toulouse, France

^h Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective: This study evaluated the success in attaining non-HDL-cholesterol (non-HDL-C) goals in the multinational L-TAP 2 study.

Methods: 9955 patients ≥ 20 years of age with dyslipidemia on stable lipid-lowering therapy were enrolled from nine countries.

Results: Success rates for non-HDL-C goals were 86% in low, 70% in moderate, and 52% in high-risk patients (63% overall). In patients with triglycerides of >200 mg/dL success rates for non-HDL-C goals were 35% vs. 69% in those with ≤ 200 mg/dL ($p < 0.0001$). Among patients attaining their LDL-C goal, 18% did not attain their non-HDL-C goal. In those with coronary disease and at least two risk factors, only 34% and 30% attained respectively their non-HDL-C and LDL-C goals. Rates of failure in attaining both LDL-C and non-HDL-C goals were highest in Latin America.

Conclusions: Non-HDL-C goal attainment lagged behind LDL-C goal attainment; this gap was greatest in higher-risk patients.

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1. Introduction

Plasma non-high-density lipoprotein cholesterol (non-HDL-C) represents the cholesterol within pro-atherogenic lipoproteins containing apolipoprotein B [1]. Non-HDL-C is an independent marker of the risk of cardiovascular events [2,3]. A meta-analysis has shown that reduction of non-HDL-C levels prevents cardiovascular events independently of changes in low-density lipoprotein cholesterol (LDL-C) [4]. The non-HDL-C was introduced in the U.S. National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) as a secondary lipid goal in addition to LDL-C. This recommendation mainly applies to patients with plasma triglycerides (TG) of >200 mg/dL, and also pertains to patients with known coronary heart disease (CHD) [5]. The importance of non-

HDL-C was recently recognized in both Canadian [6] and European Atherosclerosis [7] guidelines. However, little is known about international patterns of non-HDL-C as well as achievement of non-HDL-C goals.

The Lipid Treatment Assessment Project 2 (L-TAP 2) was a multicenter survey of lipid goal attainment in dyslipidemic patients who were on stable lipid-lowering therapy at investigation sites in 9 countries (Canada, Brazil, Mexico, the USA, France, Spain, the Netherlands, South Korea, and Taiwan) between September 2006 and April 2007 [8]. This current pre-specified analysis of the L-TAP 2 survey describes the attainment of non-HDL-C goals according to the level of risk and compared with LDL-C goal attainment in the whole study population, as well as according to gender, baseline plasma TG levels (≤ 200 mg/dL vs. >200 mg/dL), and world region.

2. Methods

The methods used in L-TAP 2 have been described previously [8]. In brief, patients were eligible if they were aged ≥ 20 years, and

* Corresponding author. Unidade Clínica de Lipídeos InCor-HCFMUSP, Av. Dr. Eneas C. Aguiar 44 Segundo Andar Bloco 2 Sala 4, CEP 05403-900 Sao Paulo, Brazil. Tel./fax: +55 11 26615320.

E-mail addresses: raul.santos@incor.usp.br, rdsf@uol.com.br (R.D. Santos).

¹ On behalf of the L-TAP 2 Investigators.

if they had been treated with the same lipid-lowering therapy for ≥ 3 months. In addition to pharmacologic agents diet and exercise were also considered to be permissible lipid-lowering therapies. A venous blood sample was drawn after fasting and all samples were analyzed in a central laboratory for total cholesterol, HDL-C, and TG. LDL-C was calculated by the Friedewald formula for TG ≤ 400 mg/dL. The non-HDL-C fraction was calculated by subtracting HDL-C from total cholesterol. The metabolic syndrome was defined, according to a previously published consensus statement [9].

The NCEP ATP III guidelines were used for patients in the USA, Latin America, and Asia [5]; the 2007 Joint European guidelines were used for European countries [10]; and the 2003 Canadian guidelines were used for patients in Canada [11]. Patients were classified into low (having one risk factor or less), moderate (having ≥ 2 risk factors), and high-risk groups (having CHD or other atherosclerotic vascular disease, or diabetes). Very high-risk patients were considered to be those with CHD plus two other risk factors.

For this analysis, the primary endpoint was success rate, defined as the proportion of patients achieving non-HDL-C treatment goals according to the NCEPATP III (5). These goals are 30 mg/dL above the LDL-C goal for each level of risk: respectively <190 mg/dL, <160 mg/dL, <130 mg/dL, and <100 mg/dL for low, moderate, high and very high risk. The prevalence of patients attaining non-HDL-C goals were evaluated overall, for each level of risk, and for those with TG levels ≤ 200 mg/dL vs. >200 mg/dL, diabetes, CHD, and CHD plus two additional risk factors. The percentages of patients who were already at their LDL-C goals but not at their non-HDL-C goals were also determined. Non-HDL-C goals were also compared by world regions and gender. Multivariate predictors of non-HDL-C goal success rates were determined using logistic regression models. Comparisons with $p < 0.05$ were considered statistically significant.

3. Results

Table 1 shows the clinical and laboratory characteristics of the 9955 patients included according to world region. The highest non-HDL-C and TG levels and lowest use of lipid-lowering treatments were found in Latin America as compared with other world regions ($p < 0.001$).

Overall, 73% and 63% of patients attained LDL-C and non-HDL-C goals, respectively. Success rates for LDL-C were 86% in low, 74% in

moderate, and 67% in high-risk patients. Non-HDL-C success decreased with an increasing level of CHD risk and was lower in patients with diabetes (53%), high risk/CHD (52%) and CHD (43%) when compared with patients not presenting these characteristics ($p < 0.001$ for each). In those at very high CHD risk, the rates of success were 30% and 34%, respectively for LDL-C and non-HDL-C. Importantly, 18% of patients who attained the LDL-C goal failed to attain non-HDL-C goals. Conversely, among patients attaining non-HDL-C success, 11% failed to attain their LDL-C goal. Non-HDL-C success was lower in males than in females: 60% vs. 65% ($p < 0.001$).

In patients with TG of >200 mg/dL, success rates for non-HDL-C were 35% compared with 69% in those with TG of ≤ 200 mg/dL ($p < 0.0001$). Rates for non-HDL-C success were lower for all levels of CHD risk in patients with TG >200 mg/dL ($p < 0.001$). In addition, patients with higher TG levels also had a lower rate of LDL-C success: 67% vs. 74% for those with TG ≤ 200 mg/dL ($p < 0.001$).

When the rates of non-HDL-C success were evaluated by world region, success was lowest in Latin America (57%) as compared with North America (64%), Europe (63%), and Asia (62%) (all $p = 0.001$ between group comparisons). Table 2 shows the rates of concomitant LDL-C and non-HDL-C success and failure according to world region. The highest rates of failure in attaining both goals simultaneously were found in Latin America ($p = 0.001$). On the contrary, the rates of both goals success were highest in Europe ($p < 0.001$).

Web appendix Table 3 shows the odds ratio estimates for predictors of non-HDL-C success rates. After multivariate analysis the independent predictors of non-HDL-C failure were (all p values < 0.0001): male gender ($\chi^2 = 18.08$), residing in Asia or Latin America ($\chi^2 = 61.32$), diabetes ($\chi^2 = 58.33$), smoking ($\chi^2 = 55.76$), hypertension ($\chi^2 = 56.63$), family history or CHD ($\chi^2 = 71.88$), and having the metabolic syndrome ($\chi^2 = 256.01$). Only statin use was associated with a success in attaining non-HDL-C goal ($\chi^2 = 199.71$, $p < 0.0001$).

4. Discussion

This analysis of the L-TAP 2 survey shows that fewer patients attain non-HDL-C goals compared with LDL-C goals. Strikingly, differences between recommended and attained non-HDL-C levels increased with the presence of risk factors, especially metabolic syndrome, as well as with a higher level of cardiovascular risk. On the other hand statin therapy was the strongest predictor of non-

Table 1
Clinical and laboratory characteristics of 9955 study patients according to world region.

Characteristics	All population	Asia	Europe	Latin America	North America	p-value
N	9955	1949	2934	1002	4070	–
Age (years)	61.7 \pm 11.7	61.5 \pm 10.7	62.0 \pm 11.8	59.5 \pm 12.3	62.1 \pm 12.0	<0.001
BMI (kg/m ²)	28.6 \pm 6.9	25.8 \pm 3.7	28.2 \pm 4.9	28.4 \pm 4.5	30.2 \pm 9.0	<0.001
Smoker (%)	13.6	13.0	17.1	7.7	12.8	<0.001
Hypertension (%)	63.7	70.2	54.4	72.7	65.1	<0.001
Metabolic syndrome (%)	32.0	26.9	27.4	34.2	37.2	<0.001
Family history of CHD (%)	29.1	15.2	27.5	21.1	38.8	<0.001
Diabetes (%)	31.0	35.6	27.5	31.2	31.2	<0.001
Statin therapy (%)	79.4	90.7	73.9	77.8	78.3	<0.001
Non statin therapy (%)	8.3	5.1	10.5	4.7	9.2	<0.001
No therapy (%)	12.1	4.0	15.4	17.3	12.4	<0.001
Low risk (%)	8.7	10.9	29.1	24.4	18.4	<0.001
Moderate risk (%)	20.3	15.7	18.8	20.9	21.8	<0.001
High risk/CHD (%)	70.8	73.3	51.9	54.5	59.7	<0.001
Total cholesterol	183 \pm 43	170 \pm 35	194 \pm 42	191 \pm 49	179 \pm 43	<0.001
LDL-C	100 \pm 37	91 \pm 30	110 \pm 37	104 \pm 43	97 \pm 36	<0.001
HDL-C	53 \pm 15	51 \pm 13	56 \pm 15	52 \pm 14	51 \pm 15	<0.001
TG	151 \pm 86	144 \pm 66	141 \pm 69	172 \pm 95	157 \pm 100	<0.001
Non-HDL-C	130 \pm 41	119 \pm 33	137 \pm 40	139 \pm 48	128 \pm 41	<0.001

CHD-coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Plasma Lipids in mg/dL; categorical variables evaluated by χ^2 test; continuous variables compared by ANOVA.

Table 2
LDL success rates versus non-HDL-C success rates by world region in the L-TAP 2 study.

Characteristics	All population	Asia	Europe	Latin America	North America	p-value ^a
N	9926	1949	2920	988	4069	—
LDL-C success and non-HDL-C success	81.8%	79.2%	86.6%	80.2%	80.2%	<0.001
LDL-C success and non-HDL-C failure	18.1%	20.7%	13.3%	19.7%	19.7%	<0.001
LDL-C failure and non-HDL-C success	11.1%	9.3%	13.7%	6.0%	11.0%	0.001
LDL-C failure and non-HDL-C failure	88.8%	90.6%	86.2%	93.9%	88.9%	0.001

^a Comparison among world regions by chi² test.

DHL-C success. When different world regions were compared, success rates were lowest for Latin American patients.

Non-HDL-C is a simple marker of the presence of pro-atherogenic lipoproteins and its assessment is particularly relevant given the worldwide increase in the incidence of obesity and metabolic syndrome [12]. In L-TAP 2, patients with higher TG levels failed to reach both non-HDL-C and LDL-C goals more often for any given level of risk compared with those with TG \leq 200 mg/dL. Indeed, in L-TAP 2, the presence of metabolic syndrome was the most important determinant of failure to attain the non-HDL-C goal.

The evidence that LDL-C reduction lowers cardiovascular disease is overwhelming and justifies setting LDL-C as the primary goal of lipid-modifying therapy [13]. However, evidence from more than 300,000 individuals without vascular disease [2], and the pooled analysis of 18,889 secondary prevention patients [3] has clearly shown that increased non-HDL-C levels are independent risk factors for cardiovascular disease. The finding that almost 20% of L-TAP 2 patients who reached their LDL-C goals persisted with increased non-HDL-C concentrations suggests that more aggressive lipid-lowering therapy in this subset of individuals would further reduce their risk.

4.1. Previous studies

The NEPTUNE II study evaluated patients from different clinical practices in the USA, and found that success rates for combined LDL-C and non-HDL-C goals were 39% for patients with a TG of \geq 200 mg/dL [14]. Recently, Virani et al. [15] evaluated CHD patients from a U.S. Hospital network. LDL-C goal attainment was 80% and, for patients with TG \geq 200 mg/dL, 51% attained both LDL-C and non-HDL-C goals. Our results confirm the results of the latter U.S. surveys and show that the lower rate of attainment of the latter lipid goals is not a problem restricted to the USA. The observation that Latin America has the highest rates of failure to attain both LDL and non-HDL-C goals may be explained by that this region has the lowest use of pharmacologic treatment and the second highest prevalence of the metabolic syndrome.

4.2. Clinical implications

The persistently elevated non-HDL-C especially in those at higher risk of cardiovascular events is almost certainly associated with an increased chance of disease recurrence even after reduction of LDL-C [3]. In the L-TAP 2 survey, the use of statin therapy was the strongest predictor of non-HDL-C success. Therefore, the use of more potent statins, in adequate doses, is indicated for controlling both LDL-C and non-HDL-C.

In conclusion, this analysis of the multinational L-TAP 2 survey has shown that many patients who reached their LDL-C goal had persistently elevated non-HDL-C levels. Hopefully, more recent recommendations [6,7] will lead to improvements in both LDL-C and non-HDL-C control worldwide.

Disclosures

RDS has received honoraria for speaking engagements and consulting fees from AstraZeneca, Merck/Schering-Plough, Novartis, Novo-Nordisk, Isis-Genzyme, Biobab, Abbott, Lilly and Pfizer Inc. DDW has received honoraria for speaking engagements and consulting fees from Anthera, Cortria, Genentech, Merck/Schering-Plough, and Pfizer Inc., and owns Anthera stock options. LT and MM are employees of Pfizer Inc. JWJ has received research grants and speaker's fees from Astellas, AstraZeneca, Biotronik, Boston Scientific, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck/Schering-Plough, Pfizer Inc., Orbus Neich, Novartis, Roche, Servier, Sanofi Aventis, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Community Framework KP7 Programme. CWC has no potential conflicts of interest to disclose. JF has received consulting fees from Merck/Schering-Plough and Pfizer Inc.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.atherosclerosis.2012.06.052>.

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