Optimal cut-off points after a daily meal corresponding to fasting goal levels of LDL-C and non-HDL-C in Chinese patients with coronary heart disease

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Abstract

Background: Although the detection of non-fasting blood lipids has been recommended in patients with coronary heart disease (CHD), the non-fasting cut-off points corresponding to the fasting goals of LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L, respectively, have not been explored.

Methods: This study enrolled 397 inpatients with CHD. One hundred and ninety-seven patients took statins for < 1 month (m) or did not take any statin before admission (i.e. CHD1 group), while 204 patients took statins for ≥ 1 m before admission (i.e. CHD2 group). Blood lipid levels were measured at 0 h, 2 h, and 4 h after a daily breakfast.

Results: Non-fasting low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C) levels significantly decreased after a daily meal ($P < 0.05$). Both fasting and non-fasting LDL-C or non-HDL-C levels were significantly lower in the CHD2 group. The percent attainment of LDL-C < 1.8 mmol/L at 2 h or 4 h after a daily breakfast was significantly higher than that of its fasting point ($P < 0.05$), whereas that of non-HDL-C < 2.6 mmol/L was significantly higher only at 4 h ($P < 0.05$). Analysis of c-statistic showed that non-fasting cut-off points for LDL-C and non-HDL-C were 1.5 mmol/L and 2.4 mmol/L, corresponding to their fasting goal levels of 1.8 mmol/L and 2.6 mmol/L, respectively. When postprandial LDL-C and non-HDL-C goal attainments were re-evaluated by non-fasting cut-off points, there were no significant differences in percent attainment between fasting and non-fasting states.

Conclusions: Determination of non-fasting cut-off points is important to evaluate the efficacy of cholesterol-lowering therapy if blood lipids are detected after a daily meal.

1. Introduction

Elevated cholesterol level is an independent risk factor for coronary heart disease (CHD). To reduce the risk of ischemic events, fasting level of low-density lipoprotein cholesterol (LDL-C) should be controlled to < 1.8 mmol/L as the primary target, then that of non-high-density lipoprotein cholesterol (non-HDL-C) should be < 2.6 mmol/L as the secondary target of cholesterol control [1–5]. It is increasingly believed that atherosclerosis is a postprandial phenomenon because, at least with respect to lipids, we are in the postprandial phase for the most part of the day [6]. Considering that either fasting or non-fasting (i.e. postprandial) LDL-C level has a similar predictive value for all-cause death and cardiovascular death [7, 8], non-fasting lipids detection at a random time-point within at least 8 h after a daily meal has been recommended in the primary and secondary prevention against CHD [9–12]. However, both LDL-C and non-HDL-C levels show a tendency of decrease in the non-fasting state [13–15]. Moreover, there are only fasting cholesterol-lowering targets but not non-fasting ones in the published guidelines [1–4, 9–12]. It is uncertain whether these fasting targets are applicable to assessing cholesterol control as well as how to evaluate it in the non-fasting stage.

Recently, we observed more substantial reductions in LDL-C and non-HDL-C levels in Chinese subjects with CHD at 2 h and 4 h after a daily breakfast [13, 16], appearing to be greater than those reported in large-scale clinical studies conducted in other countries [14, 15, 17, 18], although the potential cause remains uncertain. Additionally, it was proposed that non-HDL-C level may be a better prognostic factor than LDL-C level to evaluate the risk of future cardiovascular events [19–24]. Furthermore, non-fasting fluctuation of non-HDL-C level seem to be smaller than that of LDL-C [24]. Nevertheless, there have been no studies comparing the goal attainment of LDL-C with that of non-HDL-C in the non-fasting state.

Therefore, this study aimed to compare the percent attainments of fasting and non-fasting LDL-C and non-HDL-C reaching their fasting targets in CHD patients receiving short-term statins therapy. Furthermore, analysis of c-statistic or receiver operating characteristic curve (ROC) analysis was used to determine the non-fasting cut-off points corresponding to their fasting targets, and the percent attainments of non-fasting LDL-C and non-HDL-C were re-evaluated according to the non-fasting cut-off points.

2. Methods

2.1 Study population

From March 2017 to July 2019, 397 inpatients with CHD were enrolled from the Department of Cardiovascular Medicine of the Second Xiangya Hospital, Central South University. A total of 193 patients took statins < 1 month (m) or did not take any statin before admission (i.e. CHD1 group), and 204 patients took statins $\geq$ 1 m before admission (i.e. CHD2 group). CHD was defined as a history of myocardial infarction and/or angiographically proven coronary atherosclerosis in patients with angina pectoris.

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval. Informed consent was obtained from all participants.

2.2 Specimen collection

All enrolled participants ate breakfast between 7 a.m. and 8 a.m. according to their regular diets after overnight fast for at least 8 h. Their breakfasts were purchased from the various cafeterias in the hospital or were brought from home, rich in high-carbohydrate content, such as steamed bread, noodles, vermicelli, rice porridge, and others. Venous blood samples were collected before (0 h) and at 2 h and 4 h after breakfast.

2.3 Determination of blood lipid levels

Serum total cholesterol (TC) and triglyceride (TG) levels were measured using automated enzymatic assays. Serum high-density lipoprotein cholesterol (HDL-C) and LDL-C levels were measured using a chemical masking method [25]. All measurements, including that of albumin, were carried out on a fully

automatic biochemical analyser (Hitachi 7170A, Hitachi Inc., Tokyo, Japan) and performed by a specialist who was unaware of the details of the study [26]. Non-HDL-C = TC - (HDL-C).

2.4 Statistical analysis

Data were analysed using SPSS version 19.0. (IBM Corp., Armonk, NY, USA) and Prism 6.0 (GraphPad Inc., San Diego, CA, USA). Quantitative variables were expressed as mean $\pm$ standard deviation, and qualitative variables were expressed as numbers and percentages. The unpaired Student's t-test and chi-square test were used to analyse quantitative and qualitative variables, respectively. The optimal cut-off points for fasting LDL-C (1.8 mmol/L) and non-HDL-C (2.6 mmol/L) were determined using receiver operating characteristic (ROC curve) analysis. Based on the ROC curve, values determined using Youden analysis were used as cut-off points. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Clinical characteristics and fasting blood lipids in two CHD groups

The baseline characteristics of the CHD patients are shown in Table 1. Both groups were similar in terms of age, sex, body mass index, percentages of hypertension, current smoking, and diabetes mellitus. There were 56.5% patients taking statins < 1 m and 43.5% patients without statins treatment before admission in CHD1 group. Fasting serum levels of TC, LDL-C, and non-HDL-C in CHD2 group were significantly lower than those in CHD1 group ($P < 0.05$). The differences in fasting serum TG and HDL-C levels between the groups did not differ significantly (Table 1).

Table 1
Baseline characteristics of the study population.

	CHD1 (n = 193)	CHD2(n = 204)
Age, y	60.3 ± 9.3	62.0 ± 8.7
Men, n(%)	156(80.8)	157(77.0)
BMI, kg/m ²	24.9 ± 3.0	24.9 ± 3.0
Hypertension, n(%)	141(73.1)	152(74.5)
current smoking, n(%)	110(57.0)	103(50.5)
DM, n(%)	51(26.4)	67(32.8)
taking statins, n(%)	0	204(100) *
statins ≥ 1 m	109(56.5)	0*
statins < 1 m	84(43.5)	0*
no stains, n(%)	1.94 ± 1.46	1.74 ± 1.10
TG, mmol/L	4.10 ± 1.04	3.78 ± 1.00*
TC, mmol/L	1.01 ± 0.25	1.01 ± 0.24
HDL-C, mmol/L	2.57 ± 0.90	2.31 ± 0.88*
LDL-C, mmol/L	3.09 ± 0.96	2.77 ± 0.97*
non-HDL-C, mmol/L		

Abbreviations: CHD1 group: CHD patients taking stains < 1 m and without stains treatment before admission. CHD2 group: CHD patients taking stains ≥ 1 m before admission. BMI, body mass index; DM, diabetes mellitus; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein. *P < 0.05 when compared with CHD1 group.

3.2 Comparison of changes in non-fasting blood lipids in the two groups

Levels of TC, LDL-C, HDL-C, and non-HDL-C decreased significantly at 2 h and 4 h after a daily breakfast, while those of TG increased significantly at 4 h in the two groups and at 2 h in CHD2 group (P < 0.05). Non-fasting levels of TC, LDL-C, and non-HDL-C in CHD2 group were significantly lower than those in CHD1 group (P < 0.05) (Fig. 1A-C). However, the differences in non-fasting levels of TG and HDL-C between the groups were not statistically significant (Fig. 1D, E).

3.3 Non-fasting reductions in LDL-C and non-HDL-C levels in the two groups

When the data at 2 h and 4 h after a daily meal were pooled as whole non-fasting data for further analysis, non-fasting reductions in LDL-C were 0.47 mmol/L and 0.46 mmol/L, and non-HDL-C were 0.26 mmol/L and 0.24 mmol/L in CHD1 and CHD2 groups, respectively. The percentages of reduction in LDL-C were 17.1% and 18.5%, and 7.2% and 7.7% in non-HDL-C in CHD1 and CHD2 groups, respectively. There were no significant differences in the absolute reduction or percentage of reduction in LDL-C or non-HDL-C level between the groups. However, non-fasting reductions in LDL-C were greater than those of non-HDL-C (Fig. 2A, 2B).

Non-fasting albumin levels were measured in 89 patients among all CHD patients. There was no significant change in the albumin level after a daily breakfast (Fig. 2C), whereas the postprandial LDL-C level dropped significantly (P < 0.05) (Supplement: Table 1).

3.4 Evaluating goal attainments of LDL-C and non-HDL-C according to various targets in CHD2 group

Considering the effect of significant reduction in LDL-C or non-HDL-C level after a daily meal on the non-fasting evaluation of goal attainment, the cut-off points in non-fasting state corresponding to fasting LDL-C goal < 1.8 mmol/L and non-HDL-C goal < 2.6 mmol/L were determined by ROC analysis. Data at 2 h and 4 h after a daily breakfast were pooled as the postprandial data for a whole analysis. ROC analysis showed that non-fasting cut-off points for LDL-C and non-HDL-C were 1.5 mmol/L and 2.4 mmol/L, corresponding to their fasting goal levels of 1.8 mmol/L and 2.6 mmol/L, respectively (Figure. 3A, B).

According to the recommended targets of LDL-C and non-HDL-C in the 2016 Chinese guidelines [2], the percent attainment of LDL-C < 1.8 mmol/L in the fasting state was significantly lower than that of non-HDL-C < 2.6 mmol/L (35.3% vs 53.8%, $P < 0.001$). After a daily breakfast, the percent attainment of non-HDL-C was higher than that of LDL-C at each non-fasting time point; however, the difference was not statistically significant. The percent attainment of LDL-C at 2 h or 4 h was significantly higher than its fasting value ($P < 0.05$), while only that of non-HDL-C at 4 h was significantly higher than its fasting value ($P < 0.05$). The percent attainments of LDL-C and non-HDL-C simultaneously reaching their targets were very close to that of LDL-C not only in the fasting state but also in the non-fasting state (Fig. 3C).

According to the non-fasting cut-off points, the percent attainment of LDL-C < 1.5 mmol/L at 2 h or 4 h was 28.9% or 34.3%, which was close to the percent attainment of LDL-C < 1.8 mmol/L in the fasting state. Similar phenomenon was found for non-HDL-C, i.e., the percent attainment of non-HDL-C < 2.4 mmol/L at 2 h or 4 h was close to the percent attainment of LDL-C < 1.8 mmol/L in the fasting state. Moreover, the percent attainment of LDL-C < 1.5 mmol/L was significantly lower than that of non-HDL-C < 2.4 mmol/L at 2 h or 4 h (Fig. 3D).

According to the 2019 European guidelines, a stricter LDL-C goal < 1.4 mmol/L has been recommended for CHD patients [27]. However, there were only 22 patients (10.8%) with fasting LDL-C < 1.4 mmol/L in CHD2 group. This number of patients was too small to conduct further analysis to determine the non-fasting cut-off point corresponding to fasting LDL-C < 1.4 mmol/L.

4. Discussion

In this study, we found that when LDL-C goal < 1.8 mmol/L and non-HDL-C goal < 2.6 mmol/L were used for evaluating cholesterol control in Chinese CHD patients after short-term statins treatment, the target percentage attainment in the non-fasting state was significantly higher than that of the fasting state, suggesting that fasting targets were not suitable for the evaluation of postprandial goal attainment. To our knowledge, this is the first investigation using ROC analysis to determine the non-fasting LDL-C and non-HDL-C cut-off points corresponding to the fasting LDL-C and non-HDL-C target levels of 1.8 mmol/L and 2.6 mmol/L, respectively. Notably, according to the non-fasting cut-off points, the non-fasting goal

attainment of LDL-C or non-HDL-C was close to its fasting value evaluated by LDL-C goal < 1.8 mmol/L or non-HDL-C goal < 2.6 mmol/L. This suggests that lower non-fasting targets could be needed to evaluate the efficacy of cholesterol-lowering therapy in the non-fasting state, particularly when fasting blood lipids are unavailable and the percentage reduction of LDL-C cannot be determined due to a lack of baseline non-fasting levels before treatment.

There are two targets to evaluate the efficacy of cholesterol-lowering treatment in CHD patients. First, LDL-C should achieve a $\geq 50\%$ reduction from baseline or a goal < 1.8 mmol/L according to the European and American guidelines [3, 4], similar to the 2016 Chinese guidelines [2]. These recommendations refer only to cholesterol control in the fasting state. In this study, the goal attainment of LDL-C reduction $\geq 50\%$ could not be evaluated because the baseline fasting or non-fasting LDL-C levels before treatment could not be obtained in most patients in the CHD2 group. Under these circumstances, a physician can only make clinical judgments based on LDL-C goal levels. A considerable number of CHD patients from other locations visit physicians but forget to remain in a fasting state. This is a common situation in the outpatient department of our hospital. As a result, physicians have to assess cholesterol control using non-fasting measurement of blood lipids. According to the joint consensus statement of European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine [9], the non-fasting detection of blood lipids can be routinely applied in CHD patients as long as they are willing to undergo non-fasting measurement. This suggests that measurement of LDL-C level in the non-fasting state is quite important.

Compared with some studies with large population in other countries [14, 15, 17, 18], the reduction in LDL-C level in CHD patients after a daily meal was more significant in the present study. The maximum mean reduction in LDL-C or non-HDL-C was approximately 0.1–0.2 mmol/L in the European and North American subjects [14, 15, 17, 18]; however, Chinese CHD patients in this study showed a greater decrease in either directly detected LDL-C (i.e., 0.4–0.5 mmol/L) or calculated non-HDL-C (i.e., 0.2–0.3 mmol/L) after a daily breakfast. Although our recent study showed that the postprandial decline (i.e., 0.3–0.4 mmol/L) in calculated LDL-C was less than that of the directly detected LDL at 2–4 h after a daily breakfast in Chinese CHD patients [13], it was still more than the reduction of above the European and North American studies [14, 15, 17, 18]. The underlying mechanisms of non-fasting reduction in LDL-C may be complicated in the present study. First, in the Copenhagen General Population Study, they compared blood lipids levels of individuals at random time points after the last meal in the large-scale population. By contrast, our measurements were acquired from the same individuals at various times since the last meal, which was different from the Copenhagen General Population Study in terms of the observation time-points and monitoring method. Second, postprandial reduction in LDL-C concentration is most likely haemodilution resulting from fluid intake in relation to the meal and thus adjusting the data for albumin concentration was recommended [11, 14]. Langsted et al. [14] observed that the non-fasting LDL-C concentration no longer changed after adjustment for albumin concentration. However, a very slight change in the postprandial albumin level was observed in our study; therefore, haemodilution may not be the only cause of postprandial decline in the LDL-C level in the Chinese. Third, the diet structures of Chinese and western people are very different. For example, the Chinese people prefer carbohydrates [16].

It is not clear whether the high-carbohydrate diet will cause a more significant decline in cholesterol. At any rate, the obvious decrease in non-fasting LDL-C might affect the evaluation of goal attainment when the LDL-C level was detected after a meal.

Indeed, it was found that the percent attainment of postprandial LDL-C or/and non-HDL-C was significantly higher than that of fasting values in the present study, suggesting that the fasting goals of LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L were indeed unsuitable for the evaluation of postprandial cholesterol control. ROC analysis has been used to identify the optimal cut-off point for the diagnosis of postprandial hypertriglyceridemia [16, 28, 29] but not for determining goals of LDL-C and non-HDL-C in the non-fasting state corresponding to the fasting goals. Because the non-fasting cut-off points acquired by ROC analysis corresponded to the fasting goals of LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L, the postprandial percent attainments were very similar to their respective fasting values. This suggested that lower postprandial cut-off points, different from the fasting goals, should be adopted in the evaluation of postprandial goal attainment, unless it is possible to assess the percentage reduction in the non-fasting LDL-C level.

Non-HDL-C represents the cholesterol content of all atherosclerotic lipoproteins in the circulation, including chylomicrons, very-low-density-lipid and their remnants, intermediate-density lipoproteins, LDL, and lipoprotein (a) particles. Takahiro found that non-HDL cholesterol levels were clearly associated with future mortality and were less affected by fasting status or serum triglyceride levels [30]. Meta-analyses and prospective studies with large populations supported the opinion that on-treatment levels of non-HDL-C were stronger than that of LDL-C for future CVD risk estimation [20, 21]. Therefore, some scholars proposed that the clinical benefit obtained from controlling non-HDL-C would be greater than the one obtained from controlling LDL-C [19–21, 23]. In this study, the non-fasting reduction in non-HDL-C was less than that in LDL-C and the difference between fasting and non-fasting percentage attainments of non-HDL-C < 2.6 mmol/L was less than that of LDL-C < 1.8 mmol/L. This appears to support the superiority of non-HDL-C in contrast to LDL-C in the lipid-lowering evaluation after a daily meal. Nevertheless, the percent attainment of non-HDL-C was higher than that of LDL-C in both fasting and non-fasting states according to the goals of LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L, respectively, in this study. Overestimation of the target attainment of cholesterol control after treatment could occur if only the non-HDL-C level was evaluated.

The difference between non-HDL-C and LDL-C will increase with TG elevation, which could exert a substantial influence on evaluation of cholesterol-lowering treatment [31, 32]. The fixed difference between fasting non-HDL-C and LDL-C goals was 30 mg/dl (i.e., 0.8 mmol/L) when fasting TG level was 1.7 mmol/L, reflecting the fact that cholesterol content within TG-rich lipoproteins was about $1.7/2.2 \approx 0.8$ mmol/L. Some scholars found that the goal attainment of non-HDL-C was higher than that of LDL-C when fasting TG was < 1.7 mmol/L, while it was less than that of LDL-C when fasting TG > 2.3 mmol/L [31]. This is consistent with our findings that the percent attainment of LDL-C < 1.8 mmol/L was significantly lower than that of non-HDL-C < 2.6 mmol/L in the fasting state; however, the difference in percent attainment between LDL-C and non-HDL-C after a daily breakfast became smaller with the

increase in non-fasting TG level. Other scholars reported that the specific and fixed goals as non-HDL-C 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C goals were not sufficient for Chinese patients with CHD and proposed that flexible goals basing on TG level were more appropriate [32]. In this study, the difference (1.5 mmol/L vs. 2.4 mmol/L) between non-fasting cut-off points of LDL-C and non-HDL-C was 0.9 mmol/L corresponding to non-fasting TG level of approximately 2.0 mmol/L (i.e. $0.9 \times 2.2 = 1.98 \approx 2.0$). This suggests that a larger difference between LDL-C and non-HDL-C should be considered in the evaluation of non-fasting goal attainment even after a daily meal without high fat.

This study had some limitations. First, it was a single centre study with a small sample size of inpatients but not outpatients. In the future, the suitability of non-fasting cut-off points in a large sample of arteriosclerotic cardiovascular disease patients, including patients with ischemic stroke and peripheral vascular disease, is worth exploring. Second, only the percent attainment of the goal, but not percentage reduction of LDL-C, was evaluated because of the lack of baseline levels of blood lipids. Third, according to the recommendation of the 2019 European guidelines [27], more patients with fasting LDL-C < 1.4 mmol/L should be enrolled in CHD2 group to determine a stricter non-fasting cut-off point through ROC analysis in further study.

5. Conclusion

In conclusion, lower non-fasting cut-off points are needed to evaluate the efficacy of cholesterol-lowering therapy after a daily meal if the percentage reduction of LDL-C cannot be evaluated.

Abbreviations

CHD: coronary heart disease; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Non-HDL-C: non-high-density lipoprotein cholesterol; ROC curve: receiver operating characteristic

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University and informed consent was gained from all participants.

Consent for publication

Not applicable

Availability of data and material

The datasets analyzed during the current study are available from the corresponding

author on reasonable request

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Li-Ling Guo, Yan-qiao Chen and Ling Liu carried out the experimental work and the data collection and interpretation. Qiu-zhen Lin, Feng Tian, Qun-Yan Xiang and Li-yuan Zhu participated in the design and coordination of experimental work, and acquisition of data. Ling Liu participated in the study design, data collection, analysis of data and preparation of the manuscript. Li-Ling Guo and Ling Liu carried out the study design, the analysis and interpretation of data and drafted the manuscript. All authors read and approved the final manuscript

Acknowledgments

Not applicable

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Figures

Figure 1

Comparison of changes in non-fasting blood lipids in two groups. Non-fasting changes in serum levels of TC (A), LDL-C (B), non-HDL-C (C), TG (D) and HDL-C (E). CHD1 group: CHD patients taking stains <1m and without stains treatment before admission. CHD2 group: CHD patients taking stains $\geq$ 1m before admission. Values are means with SE. # $P < 0.05$ when compared with the fasting level in the same group. * $P < 0.05$ when compared with CHD1 group at the same time point.

Figure 2

Non-fasting reductions in LDL-C and non-HDL-C levels in two groups. (A) Comparison of non-fasting absolute reductions in LDL-C and non-HDL-C levels. (B) Comparison of non-fasting percentages of reductions in LDL-C and non-HDL-C levels. CHD patients including patients in CHD1 group and CHD2 group. (C) Levels of LDL-C and albumin as a function of time since breakfast in 89 CHD patients. Values are means with SE. * $P < 0.05$ when compared with the absolute reduction or percentage of reduction in non-HDL-C level. # $P < 0.05$ when compared with the fasting level. CHD1 group: CHD patients taking stains $< 1m$ and without stains treatment before admission. CHD2 group: CHD patients taking stains $\geq 1m$ before admission.

Figure 3

Comparison of the percent attainments of LDL-C and non-HDL-C levels according to different targets in fasting and non-fasting states in Group CHD2. CHD2 group: CHD patients taking stains $\geq 1\text{m}$ before admission. (A, B) Non-fasting cut-off points in relation to fasting LDL-C level 1.8 mmol/L (A) and non-HDL-C level 2.6 mmol/L (B) determined by ROC analysis and Youden's index (marked by the solid arrows). (C) Comparison of the percent attainments in both fasting and non-fasting states according to the recommended targets of LDL-C level $< 1.8 \text{ mmol/L}$ and non-HDL-C level $< 2.6 \text{ mmol/L}$. (D) Comparison of the percent attainments according to non-fasting cut-off points of LDL-C $< 1.5 \text{ mmol/L}$ and non-HDL-C $< 2.4 \text{ mmol/L}$. # $P < 0.05$ when compared with the percent attainment of the same target(s) in the fasting state. * $P < 0.05$ when compared with the percent attainment of different LDL-C target at the same time point.

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