Su et al. Lipids in Health and Disease (2019) 18:134
https://doi.org/10.1186/s12944-019-1080-x

Lipids in Health and Disease

REVIEW Open Access

Evidence for changing lipid management strategy to focus on non-high density lipoprotein cholesterol

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Abstract

Low-density lipoprotein cholesterol (LDL-C) has been recommended as the primary treatment target on lipid management in coronary heart disease (CHD) patients for past several decades. However, even by aggressive LDL-C lowering treatment, patients still present a significant residual risk of major adverse cardiovascular events (MACE). Non-high-density lipoprotein cholesterol (non-HDL-C) contained all the atherogenic lipoproteins, such as chylomicron, very-low density lipoprotein (VLDL), LDL, intermediate density lipoprotein (IDL). Many prospective observation studies have found that non-HDL-C was better than LDL-C in predicting risks of MACE. Since non-HDL-C appears to be superior for risk prediction beyond LDL-C, current guidelines have emphasize the importance of non-HDL-C for guiding cardiovascular prevention strategies and have flagged non-HDL-C as a co-primary therapeutic target. The goals of non-HDL-C were recommended as 30 mg/dl higher than the corresponding LDL-C goals, but the value seemed inappropriate. This review provide evidence for changing lipid management strategy to focus on non-HDL-C and appropriate values for adding to LDL-C goals would be proposed.

Keywords: LDL-C, Non-HDL-C, Goals, Coronary heart disease, Risk

Introduction

The prevalence of coronary heart disease (CHD) in both developed and developing countries has risen markedly, posing serious risks to future health of humans and leading to a high mortality [1–3]. Nowadays, the relationship between hypercholesterolemia and CHD has been well established [4–6], and lipid-lowering therapy is an important strategy in primary and secondary prevention of CHD [7, 8]. In the past few decades, low-density lipoprotein cholesterol (LDL-C) was recommended as the primary treatment target on lipid management in CHD patients [9–11]. Historically, when it comes to decreasing CHD risk, most lifestyle and pharmacologic interventions focused on reducing LDL-C. Selected worldwide dyslipidemia guidelines and expert recommendations, including the American Diabetes Association/American College of Cardiology (ADA/ACC) guidelines [12], Canadian Cardiovascular Society (CCS) guidelines [13] and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines [14], have all identified LDL-C targets of < 70 and < 100 mg/dl for patients at very high- and high-risk for CHD, respectively, and recommended the first-line therapy should be directed toward LDL-C lowering.

In contrast to LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C) receives much less attention and remains as a co-primary therapeutic target associated with LDL-C or as a secondary target when triglyceride (TG) > 200 mg/dl within current guidelines [15, 16]. Indeed, non-HDL-C quantifies all atherogenic apolipoprotein B-containing lipoproteins, including LDL, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicrons (CM), and their TG-rich lipoprotein remnants (Fig. 1), whose contribution to atherogenic risk is accounted for by non-HDL-C but not LDL-C alone [17]. Additionally, non-HDL-C is simply calculated by subtracting HDL-C from total cholesterol (TC) [18] and is not influenced by fasting conditions, which could provide convenience for patients [19]. For these reasons, the significance of non-HDL-C in predicting CHD risks is being well

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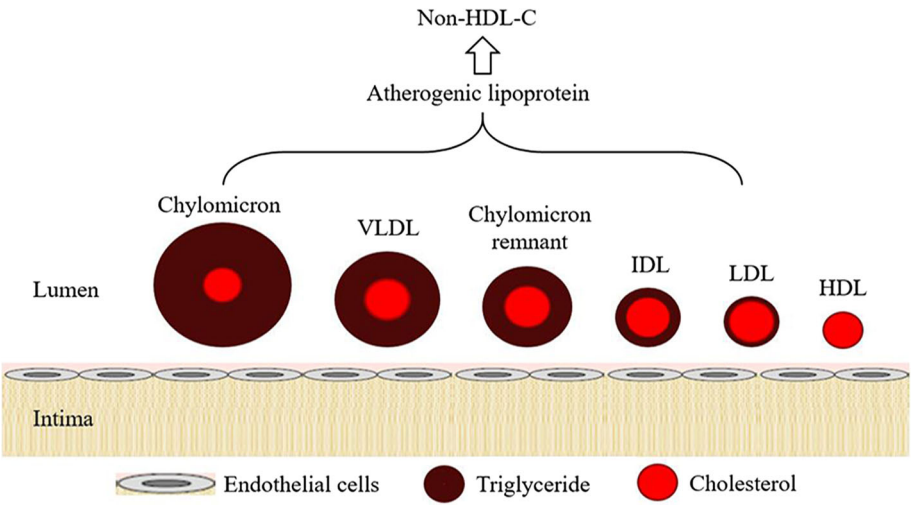

Fig. 1 Important lipids in human plasma. Non-HDL-C, calculated as [total cholesterol – (HDL-C)], quantifies all atherogenic apolipoprotein B-containing lipoproteins, including LDL, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicrons, and their TG-rich lipoprotein remnants

recognized. Currently, several important guidelines, including International Atherosclerosis Society (IAS) guideline [20], National Lipid Association (NLA) guideline and National Institute for Health and Care Excellence (NICE) guideline [21], have flagged non-HDL-C as a primary therapeutic target for patients with CHD. However, whether non-HDL-C or LDL-C is the better marker reflecting the atherogenic coronary risk remains controversial.

Residual risk of CHD beyond LDL-C after using lipid-lowering therapy

It is no doubt about the relationship between plasma levels of LDL-C and risks of CHD, as well as about the benefits of lipid-lowering therapy such as statin treatment. Over the past two decades, several large-scale randomized controlled trials, including the Scandinavian Simvastatin Survival Study (4S) [22, 23], the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study [24, 25], the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study [26, 27], have demonstrated the beneficial effects of statins in lowering the risk of CHD. As such, lipid-lowering agents have become a mainstay of therapy in the primary and secondary prevention of major adverse cardiovascular events (MACE) [28–31]. However, despite the success of LDL-C lowering, it is also clear from the evidence that the persistence of a high CHD risk, as a concept called residual risk, are notable after using lipid-lowering agents [32–34].

There is evidence that even achieving lower LDL-C targets (< 70 mg/dl) recommended by current guidelines in very high-risk patients may still leave a high residual risk of MACE. In the 4S trial, patients treated with statin therapy experienced CHD event rates approximating 19% (compared to 28% with placebo) over the 5-year study period [35, 36]; in the Cholesterol and Recurrent Events (CARE) trials, plasma LDL-C of patients with 40 mg pravastatin each evening reduced during follow-up by 28%, but the residual risk of MACE remained 10.2% compared to 13.2% in patients with placebo [37, 38]. Similar results were observed in other studies such as the Heart Protection Study (HPS) [39–41]. Additionally, a meta-analysis including 90,056 individuals from 14 randomized trials reported that statin therapy reduced the risk of major vascular events by 23% for each 1 mmol/L LDL-C lowering. However, the residual risk of MACE over a 5-year period remained high; 14% of patients experienced a cardiovascular event despite being allocated to the statin group, compared with 18% among patients allocated to placebo [42].

The subsequent analyses evaluated the effects of high-dose statin treatment for more intensive LDL-C lowering. In the Treating to New Targets (TNT) trial, where treatment with atorvastatin 80 mg daily was associated with a 22% relative risk reduction of MACE compared with treatment with atorvastatin 10 mg daily, one in 11 patients experienced a cardiovascular event during 5-years follow-up; in the Pravastatin or Atorvastatin Evaluation and Infarction Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI22) and the Incremental Decrease in Endpoint through Aggressive Lipid Lowering (IDEAL) trials, high-intensity (80 mg atorvastatin daily) therapy demonstrated greater CVD risk reduction when compared to moderate-intensity statin therapy, but residual risk in the intensive treatment arms was still 22.4 and 12%, respectively, despite mean LDL-C levels that were not elevated [43–45]. Since the persistently residual CHD risk despite high-intensity statin therapy, the consideration of adjunctive therapies has been prompted to reduce further risk of CHD. Indeed, the IMProved Reduction of Outcomes:

Vytorin Efficacy International Trial (IMPROVE-IT) was designed to assess the benefits of ezetimibe to moderate-intensity simvastatin. Once again, the rate of MACE decreased significantly, but patients in the treatment by lipid-lowering agents still presented a 32.7% residual risk (compared to 34.7% with simvastatin alone) [46–48].

More recently, Nichols et al. determine whether high TG in the presence of statin-controlled LDL-C influence the risk of CHD among patients with diabetes by using the data about adults with diabetes from the Southern California and Pacific Northwest regions of Kaiser Permanente. The incidence rate for non-fatal MI was 30% higher in the high TG group [Rate Ratio (RR) =1.30; 95% CI, 1.08~1.58]. The rate was 23% higher for non-fatal stroke (1.23, 1.01~1.49), 21% higher for coronary revascularization (RR = 1.21; 95% CI, 1.02~1.43) and 33% higher for unstable angina (RR = 1.33; 95% CI, 0.87~2.03) [49]. We can infer from these results that TG levels might lead to the excess risk of MACE in patients with high level of TG. Thus, even the LDL-C level was controlled by lipid-lowering agents, rate of MACE was greater among patients with diabetes and high TG levels.

Non-HDL-C as a better predictor for CHD

Almost all currently available guidelines have stressed that LDL-C levels should be used as the primary target to lipid-lowering therapy. However, trials about the efficacy of lipid-lowering therapy have shown that the cardiovascular benefits of statins may go beyond their influence on LDL-C levels. Thus, LDL-C may not be the best lipid parameter to predict cardiovascular risk or to quantify the athero-protective effect of lipid-lowering agents.

A number of studies have investigated the relationships between LDL-C or non-HDL-C and the risk of CHD in the past three decades. Early in 2001, data from the Lipid Research Clinics Program Follow-up Study, designed to determine whether non-HDL-C could be useful in predicting CHD mortality over a 19-year follow-up in 2406 men and 2056 women, revealed that levels of non-HDL-C at baseline was significant and strong predictors of CHD deaths while LDL-C level was a somewhat weaker predictor in both sexes. Differences of 30 mg/dl in non-HDL-C and LDL-C levels corresponded to increases in CHD risk of 19, 15% in men and 11, 8% in women, respectively. Compared with men with non-HDL-C < 160 mg/dl, those with non-HDL-C > 220 mg/dl had a hazard ratio (HR) for future CHD of 2.14 (95% CI, 2.50~3.04). Compared with men with LDL-C > 130 mg/dl, men with LDL-C > 190 mg/dl had a HR for future CHD of 1.77 (95% CI, 1.22~2.59). Results were similar among women [50].

A nested case-control study among 18,225 participants of the Health Professionals Follow-up Study was designed to compare non-HDL-C and LDL-C as predictors of CHD. After adjustment for matching factors, the relative risk of CHD in the highest quintile compared with the lowest quintile was 2.76 (95% CI, 1.66~4.58) for non-HDL-C and 1.81 (95% CI, 1.12~2.93) for LDL-C. When non-HDL-C and LDL-C were mutually adjusted, only non-HDL-C was predictive of CHD, suggesting that non-HDL-C could be more strongly associated with CHD risk than LDL-C [51]. Similarly, data from the Framingham Heart Study (2693 men and 3101 women) and showed that on the basis of the joint distributions of LDL-C and non-HDL-C, after multivariate adjustment, no association was found between LDL-C and the risk for CHD within non-HDL-C level; whereas within LDL-C levels, a strong positive and graded association between non-HDL-C and risk for CHD was observed [52].

Recently, a meta-analysis including 8 statin trials found that patients with on treatment LDL-C < 100 mg/dl but non-HDL-C > 130 mg/dl had significant a HR for future CHD of 1.32 (95% CI, 1.17~1.50) compared to those reaching both targets. In contrast, patients with on treatment LDL-C > 100 mg/dl but non-HDL-C < 130 mg/dl had similar HR for future CHD of 1.02 (95% CI, 0.92~1.12) as those reaching both targets [53]. In 2013, in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk prospective population study containing 25,639 men and women aged 45~79 years, researchers found that the multivariable-adjusted HR of future CHD was 1.22 (95% CI, 1.17~1.27) for LDL-C and 1·26 (95% CI, 1.20~1.31) for non-HDL-C, respectively. The multivariable-adjusted HR of future CHD in the highest quartile was 1.67 (95% CI, 1.47~1.91) in LDL-C and 1.87 (95% CI, 1.62~2.15) in non-HDL-C [54].

Furthermore, in 2016, Zhang et al. studied 1757 consecutive subjects undergoing coronary angiography and found non-HDL-C (HR = 1.33; 95% CI, 1.16~1.51) was slightly superior to LDL-C (HR = 1.28; 95% CI, 1.13~1.46) in predicting high severity of CHD after adjusting for potential confounders. In 2017, a retrospective study investigated the predictability of attaining non-HDL-C goal and long-term MACE in Thai patients after acute myocardial infarction (AMI) compared to attaining LDL-C target. During mean follow-up of 2.6 years among 868 patients after AMI, 34.4% achieved non-HDL-C target, 23.7% achieved LDL-C target and 21.2% experienced MACEs. Compared to those with non-HDL-C level less than 100 mg/dl, patients with non-HDL-C greater than 130 mg/dl had a HR for MACE of 3.15 (95% CI, 1.46~6.80). However, compared to those with LDL-C level less than 70 mg/dl, patients with LDL-C greater than 100 mg/dl was associated with reduced risk of MACE (HR = 0.42; 95% CI, 0.18~0.98) after direct pairwise comparison with non-HDL-C level. These results indicated that non-HDL-C was a better predictor of future MACE following AMI [55]. Another study in 2017 indicated that non-HDL-C was good predictors of the risk of increased arterial stiffness in postmenopausal women in an urban

Brazilian population [56]. Since increased arterial stiffness is an independent risk of CHD, this result also provided the evidence that non-HDL-C could better reflect the risk of CHD. In a large cohort analysis about among 62,428 statin-treated individuals with type 2 diabetes mellitus in healthcare delivery system of Kaiser Permanente Northern California, the relevance of non-HDL-C goals for primary prevention of CHD among patients with diabetes was assessed. After adjusted, the risk of incident CHD for these statin-treated patients was lower with decreasing achieved non-HDL-C levels ($P < 0.001$). Relative to achieved non-HDL-C ≥ 160 mg/dl, non-HDL-C < 80 mg/dl had HR = 0.59 (95% CI, 0.51~0.68). [57]. In a total of 13 studies with 156,381 individuals, the pooled RR of CHD was 1.59 (95% CI, 1.46~1.72) in the general population and 1.99 (95% CI, 1.57~2.51) in type 2 diabetes patients. Subgroup analysis showed the similar effect of non-HDL-C on CHD risk between men (RR 1.98; 95% CI, 1.70~2.30) and women (RR 1.63; 95% CI, 1.35~1.96) [58]. These findings support the use of non-HDL-C treatment goals for CHD primary prevention in diabetic patients. In a word, non-HDL-C was better than LDL-C in the prediction of future MACE.

Non-HDL-C as a better target of lipid-lowering therapy

As mentioned above, to address therapeutic adequacy, certain worldwide guidelines have designated secondary targets for non-HDL-C (< 100 and < 130 mg/dl) when LDL-C goal have been achieved in very high- risk and high-risk patients, respectively, with TG levels between 200~500 mg/dl. Evidence showed that the agents for lipid-lowering therapy to reduce cardiovascular risk, such as statins, also lower non-HDL-C. In 2008, a post-hoc analysis, combined data from 2 prospective and randomized clinical trials in which 10,001 patients from the TNT trial and 8888 patients from the IDEAL trial with established CHD with usual-dose or high-dose statin treatment, showed that in models with LDL-C and non-HDL-C were positively associated with cardiovascular outcomes, whereas a positive relationship with LDL-C was lost. When LDL-C and non-HDL-C were included simultaneously, the positive relationship between LDL-C and major cardiovascular events was lost, whereas non-HDL-C retained its positive association with the occurrence of such events (HR = 1.31; 95% CI, 1.19~1.44) [59]. These results indicated that in patients with lipid-lowering treatments, level of non-HDL-C was more closely associated with cardiovascular outcome than level of LDL-C. In addition, to deeply explore the relationship between non-HDL-C reduction and CHD risk reduction for various lipid-modifying therapies, Robinson et al. performed a meta-analysis and showed that for statins, each 1% decrease in non-HDL-C resulted in an estimated 4.5-year CHD relative risk of 0.99 (95% CI, 0.98~1.00), and similar results were shown by using other lipid-lowering agents such fibrate and niacin. Most lipid-modifying drugs used as monotherapy have a one to one relationship between percentage non-HDL-C lowering and CHD reduction [60].

More recently, data from 1792 individuals who underwent percutaneous coronary intervention (PCI) from January 2004 to December 2009 were analyzed by Lee. All LDL-C and non-HDL-C variability parameters were independent predictors for MACE after adjusting for potential confounding factors. The authors demonstrated that 1 standard deviation (SD) increase corrected variability independent of mean (cVIM) of LDL-C and non-HDL-C increased the risk of MACE by 34% (HR = 1.34; 95% CI, 1.18~1.52) and 37% (HR = 1.37; 95% CI, 1.20~1.57), respectively [61]. Another analysis from Tehran lipid and glucose study including 5474 participants showed that during a median follow-up of 8.9 years and after adjustment, each 1-SD increase in LDL-C and non-HDL-C was associated with 12% (HR = 1.15; 95% CI, 1.05~1.21) and 16% (HR = 1.38; 95% CI, 1.25~1.46) risk for T2DM, respectively ($P < 0.05$) [62]. These findings indicated that non-HDL-C treatment goals could be a better target of lipid-lowering therapy.

Recommended value of non-HDL-C goals

Non-HDL-C has been verified as an important target of therapy for CHD [63–65]. However, the goal of non-HDL-C still remains ambiguous. Current recommendations set the goal of non-HDL-C as 30 mg/dl higher than the corresponding LDL-C goals [66–68]. That is, a patient with a LDL-C goal of 70 mg/dl would have a corresponding non-HDL-C goal of 100 mg/dl. As mentioned above, non-HDL-C, calculated as the difference between TC and HDL-C, represents the cholesterol mass contained in all atherogenic lipoproteins including LDL-C and VLDL-C. The rationale for difference of 30 mg/dl between LDL-C and non-HDL-C goals was based on the assumption that VLDL-C was the principal atherogenic lipoprotein after LDL-C [69]. It is proposed that, on the average, the weight ratio of TG to cholesterol in VLDL particle is 5 to 1 [70]; that is, if the weight of TG is 150 mg in VLDL particle, the weight of cholesterol content in VLDL particle should be around 30 mg. Recent evidence suggested that a biologically optimal fasting TG level was less than 150 mg/dl [71–73], so a normal VLDL-C level was likely less than 30 mg/dl.

Actually, evidence from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin (LUNAR) Trial have already shown that to better match LDL-C, the current non-HDL-C goal should be lowered by 8~10 mg/dl [74]. In 2013, an analysis revealed that LDL-C cut-points of 100, 130, 160, and 190 mg/dl were in the same population percentiles as non-HDL-C values of 125, 157, 190, and 223 mg/dl in 1,310,440 U.S. adults population [75]. In 2014, Kuwabara et al. used baseline cross-sectional

data of 4110 participants from two studies: the KOBE Study and the Tsuruoka Metabolomic Cohort Study and evaluated whether the difference between LDL-C and non-HDL-C in the general Japanese population. They found the mean difference between the non-HDL-C and LDL-C was 19.6 mg/dl and 24.1 mg/dl for men for the KOBE Study and Tsuruoka Metabolomic Cohort Study, respectively [76]. Similar difference was also observed in women. In both cohort studies, the difference was lower than 30 mg/dl. More recently in 2018, Brito et al. investigated 14,837 participants from the Longitudinal Study of Adult Health (ELSA-Brasil) and also found obvious difference and discordance in Brazilian population as the non-HDL-C values, based on correspondent LDL-C population percentiles (70, 100, 130, 160, and 190 mg/dl), were 92, 122, 156, 191, and 223 mg/dl [77].

The discordance and difference between non-HDL-C and LDL-C provided the evidence that adding of 30 mg/dl to LDL-C goal as non-HDL-C goal seemed inappropriate and might over-estimate goal-reaching rate. Lowering 5~10 mg/dl of conventional non-HDL-C cut-points may better match percentiles of LDL-C cut-points. However, large-scale prospective studies in CHD patients are needed to determine the validity of the values.

Conclusions

There is significant residual risk of MACE despite aggressive lipid-lowering therapy. Accumulating evidence support that the relationship between non-HDL-C lowering and reduction of cardiovascular risk. Non-HDL-C is a more comprehensive measure of atherogenic particles than LDL-C and is superior to LDL-C in its ability to predict MACE, thus, non-HDL-C has been shown to predict CHD similarly to apolipoprotein B. We suggest that in clinical practice, more attention should be directed to non-HDL-C and to achieving non-HDL-C goals in patients at increased cardiovascular risks. In summary, given the superiority of non-HDL-C in cardiovascular risk prediction beyond LDL-C, and the proven benefit of non-HDL-C lowering, future guidelines should emphasize the importance of non-HDL-C for guiding cardiovascular prevention strategies.

Abbreviations

4S: The Scandinavian Simvastatin Survival Study; ADA/ACC: American Diabetes Association/American College of Cardiology; AMI: Acute myocardial infarction; CARE: The Cholesterol and Recurrent Events trials; CHD: Coronary heart disease; CI: Confidence interval; CM: Chylomicrons; ESC/EAS: European Society of Cardiology/European Atherosclerosis Society; HPS: The Heart Protection Study; IAS: International Atherosclerosis Society; IDEAL: The Incremental Decrease in Endpoint through Aggressive Lipid Lowering; IDL: Intermediate-density lipoprotein; IMPROVE-IT: The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; JUPITER: The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin study; LDL-C: Low density lipoprotein cholesterol; LIPID: The Long-Term Intervention with Pravastatin in Ischemic Disease study; MACE: Major adverse cardiovascular events; NICE: National Institute for Health and Care Excellence; NLA: National Lipid Association; Non-HDL-C: Non-high density lipoprotein cholesterol; PROVE IT-TIMI: The Pravastatin or Atorvastatin Evaluation and Infarction Therapy-Thrombolysis In Myocardial Infarction; RR: Rate Ratio; TC: Total cholesterol; TG: Triglyceride; TNT: The Treating to New Targets trial; VLDL: Very low-density lipoprotein

Acknowledgements

Not applicable.

Authors' contributions

D-Q Peng conceived of the scope of the review and helped draft the manuscript. X Su and Y Kong was involved in the accumulation of the relevant references and drafted the manuscript. All authors read and approved the final manuscript.

Funding

This project was supported by grants from National Natural Science Foundation of China (No.81870336 and No.81670426 to D.P.).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 7 January 2019 Accepted: 31 May 2019
Published online: 07 June 2019

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