Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol

Ahmed Abdalwahab, Ayman Al-atta, Azfar Zaman, Mohammad Alkhalil

ORCID number: Ahmed Abdalwahab 0000-0001-5221-0009; Ayman Al-atta 0000-0003-2335-9596; Azfar Zaman 0000-0003-4891-8892; Mohammad Alkhalil 0000-0002-3088-8878.

Author contributions: Alkhalil M contributed to the conceptualization, methodology and project administration; Zaman A and Alkhalil M provided the resources; Abdalwahab A and Al-atta A contributed to writing original draft and preparation; all authors finally wrote review and edited the manuscript.

Conflict-of-interest statement: The authors have no any conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited

Abstract

Statins have been shown to be effective in reducing cardiovascular events. Their magnitude of benefits has been proportionate to the reduction in low-density lipoprotein cholesterol (LDL-c). Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have further improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by LDL-c level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous, including thrombosis and inflammation risks. Moreover, the lipoprotein related risk is increasingly recognised to be related to other non-LDL-c markers such as Lp(a). Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plaques at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

Key Words: Intensive lipid-lowering; Proprotein convertase subtilisin kexin 9 inhibitors; Ezetimibe; Plaque imaging; Low-density lipoprotein cholesterol

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
manuscript

Core Tip: Intensive lipid-lowering therapies using ezetimibe and more recently proprotein convertase subtilisin kexin 9 inhibitors have improved clinical outcomes. Unselective application of these treatments is undesirable and unaffordable and, therefore, has been guided by low-density lipoprotein cholesterol level. Nonetheless, the residual risk in the post-statin era is markedly heterogeneous. Emerging data show that intensive lipid-lowering therapy produce larger absolute risk reduction in patients with polyvascular disease, post coronary artery bypass graft and diabetes. Notably, these clinical entities share similar phenotype of large burden of atherosclerotic plaques. Novel plaque imaging may aid decision making by identifying patients with propensity to develop lipid rich plaques at multi-vascular sites. Those patients may be suitable candidates for intensive lipid lowering treatment.

Citation: Abdalwahab A, Al-atta A, Zaman A, Alkhailil M. Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol. World J Cardiol 2021; 13(9): 472-482
URL: https://www.wjgnet.com/1949-8462/full/v13/i9/472.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i9.472

INTRODUCTION

Despite optimal, guideline-recommended medical therapy for secondary prevention, patients remain at increased risk of cardiovascular events. This risk, referred to as residual risk, is attributable to different processes such as lipid accumulation, inflammation, and thrombosis[1]. Estimating lipid risk has always been guided by the use of low-density lipoprotein cholesterol (LDL-c)[2]. The magnitude of LDL-c reduction was associated with proportionate decrease in cardiovascular events in response to lipid lowering treatment[3]. The Cholesterol Treatment Trialists Collaboration (CTTC) reported from 26 trials including 16938 patients that for every 1.0 mmol/L reduction in LDL-c, there was 22% reduction in cardiovascular events[3]. Importantly, these benefits were derived using HMG CoA reductase inhibitors (i.e., statins).

Recent development in lipid-lowering therapies, including ezetimibe and proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have confirmed the LDL-c hypothesis[4,5]. In other words, the reduction in cardiovascular outcomes was related to LDL-c reduction and reproduced using non-statin treatments[6-8]. Therefore, the concept of lower is better should ideally be applied to all patients with vascular disease and LDL-c should be targeted using statin alongside non-statin drugs. Nonetheless, current guidelines recommend intensifying lipid-lowering therapy using ezetimibe or PCSK9 guided by LDL-c level[2]. Whilst the recommended targets for LDL-c has been lowered to reflect the reported cardiovascular benefits from recent intensive lipid-lowering trials[6-8], such an approach may deprive a subset of patients from potential benefits in response to intensive LDL-c reduction. This Review discusses the limitations of solely using LDL-c to guide intensive lipid-lowering therapy and highlights a strategy to identify patients who would benefit from adding a second lipid-lowering treatment, mainly PCSK9 inhibitor, on top of statin.

CAVEATS OF ROUTINELY USING INTENSIVE LIPID LOWERING TREATMENT

Data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trials highlighted better cardiovascular outcomes in response to LDL-c reduction in patients on maximally-tolerated statin dose[6-8]. Notably, the magnitude of reduction in LDL-c did not match the decrease in clinical events[5,9]. This becomes more evident when comparing data of PCSK9 inhibitors to CTTC clinical outcomes[3,9]. When juxtaposed to the reduction in LDL-c level, there may be diminished benefits in response to very low LDL-c with lack of significant incremental benefits below a certain level of LDL-c[5,9]. This possible “plateau effect” was also highlighted on a
mechanistic level in the GLobal Assessment of Plaque reGression With a PCSK9 antibody as Measured by intraVascular Ultrasound (GLAGOV) trial[10]. Further reduction in LDL-c did not lead to commensurately greater plaque regression, highlighting a possible phenomenon that could be referred to as “LDL-c exhaustion”. Whether longer exposure to low LDL-c may be translated into larger plaque regression using PCSK9 inhibitors is yet to be determined. A recent large meta-analysis of 34 trials highlighted that the reduction in mortality in response to intensive lipid-lowering therapy compared to less-intensive regimen was only evident at LDL-c level of 100 mg/dL[11]. The presence of a threshold is in line with the proposed concept of “LDL-c exhaustion”, however, future studies are needed to identify the optimal threshold according to patients’ clinical syndromes.

Importantly, residual cardiovascular risk is recognised even after achieving low LDL-c[1,12] a reflection of the multiple mechanisms underlying atherothrombotic vascular disease. Almost one in ten patients had a second vascular event within 3 years follow up despite attaining LDL-c to < 70 mg/dL[7]. Therefore, using LDL-c as the only surrogate of future adverse events has significant limitations, and there is need to characterise atherosclerotic disease processes beyond estimating future cardiovascular risk. Other disease characteristics, such as thrombosis or inflammation, maybe more prominent and tailored therapies might be more effective in reducing the residual risk.

Moreover, costs may challenge the routine use of PCSK9 inhibitors in patients with cardiovascular disease. Subjecting patients to PCSK9 inhibitors guided by the FOURIER and ODYSSEY Outcomes trials criteria would incur an increase in health care costs by $450000 and $315000 per QALY, factoring in late effect on mortality[9,13-15]. The cost would remain significant even when including patients with baseline LDL-c ≥ 100 mg/dL[9,13,14].

Overall, unselective implementation of PCSK9 inhibitors is undesirable and unaffordable given the modest effect on preventing cardiovascular events at a significant increase of health costs. Therefore, adopting a new strategy based on the characteristics of the atherosclerotic disease process may be more promising. Emerging data provide new insights into the role of certain atherosclerotic features to identify patients who sustain larger clinical benefits when using intensive lipid-lowering therapy. Such features include polyvascular disease, diabetes and post coronary artery bypass graft (CABG).

**Polyvascular disease**

Polyvascular disease refers to atherosclerotic involvement of two or more of arterial vascular beds[16]. Exposure to high concentrations of low-density lipoprotein, including very small, small, intermediate and large particles was associated with developing polyvascular disease in patients with peripheral arterial disease[17]. Several trials have shown the close correlation between the number of involved vascular beds with increased mortality[18,19]. Polyvascular disease is considered as one of the high risk features in initial Task Force of European Society of Cardiology (ESC)/European Atherosclerosis Society. To mitigate the risk, commencing PCSK9 in addition to statin, was recommended, albeit, to achieve LDL-c level of < 100 mg/dL[2], and even lower according to the new European guidelines[2,20]. Nonetheless, LDL-c remains key in titrating intensive lipid-lowering therapy in this high risk group.

The IMPROVE IT trial revealed a higher cardiovascular event rates with almost 50% increased risk in cardiovascular death in patients with polyvascular compared to monovascular disease[19]. The combination of CAD and peripheral vascular disease was associated with more than 25% incidence rate of myocardial infarction[19]. Importantly, the benefits of adding ezetimibe to statin therapy were seen regardless of the number of diseased vascular beds, although patients with polyvascular disease sustained a numerically larger absolute risk reduction in response to intensive statin therapy[19]. In pre-specified subgroup analysis of the ODYSSEY Outcomes trial, alirocumab was associated with absolute risk reduction in cardiovascular events proportional to the number of diseased vascular beds i.e., 1.4% for monovascular disease, 1.9% for two beds vascular disease and 13% in three beds polyvascular disease [21]. However, in the FOURIER trial, the risk reduction associated with evolocumab was relatively modest (2.7%) in the polyvascular disease group despite having heightened residual cardiovascular risk (19.9%)[22]. The inconsistency may be related to statistical power, although other factors, such as the targeted population, definition and aetiologies of vascular disease need to be factored in when interpreting these results.
To overcome these issues, Alkhali et al.[23] conducted a meta-analysis of 7 studies including 94362 patients, reporting the role of intensive lipid-lowering therapy in polyvascular vs monovascular disease groups. They highlighted that the absolute risk reduction was more marked in patients with polyvascular disease [(6.5% (95% CI, 5.0–7.9)) compared to monovascular disease [1.8% (95% CI, 1.3–2.3)]. Notably, when the analysis was performed according to the level of baseline LDL-c, there was a differential treatment effect in response to intensive lipid-lowering therapy in patients with monovascular disease. Patients with monovascular disease and LDL-c > 100 mg/dL had absolute risk reduction of 3.2% (95% CI, 2.3–4.1) compared to 1.2% (95% CI, 0.6–1.8) in patients with monovascular disease and LDL-c ≤ 100 mg/dL. In contrast, patients with polyvascular disease had comparable treatment effects irrespective of LDL-c [5.7% (95% CI, 3.6–7.8) in patients with LDL-C >100 mg/dL and 7.2% (95% CI 5.2–9.2) in those with LDL-C ≤ 100 mg/dL][23]. Moreover, recent data from the ODYSSEY Outcomes trial suggest that the magnitude of LDL-c reduction across the strata of evident vascular disease was comparable, yet, the reduction in clinical outcomes was more pronounced in those with polyvascular disease[21]. This was in contrast with CTTC data whereby lowering LDL-c was associated with a consistent reduction in vascular events among patients with different clinical characteristics[24]. Collectively, this may suggest that monitoring response to intensive lipid-lowering therapy can no longer be guided using LDL-c in the post statin era. A notion that was recently highlighted from the Copenhagen General Population Study.

PATIENTS WITH PRIOR CABG

Patients with previous CABG have extensive coronary artery disease and are at increased risk of adverse cardiovascular events, including mortality[25,26]. Early data showed the beneficial effect of statins in patients with previous CABG[27]. More recently, aliroculumab was reported to have heterogeneity in treatment effects according to the status of previous CABG. The absolute risk reduction of major adverse events was remarkably larger [6.4%, (95% CI: 0.9 to 12.0)] in patients with CABG compared to those with no previous CABG [1.3%, (95% CI: 0.5 to 2.2)][28].

Similar outcomes were reported in the pre-specified analysis from the IMPROVE IT trial[29]. Adding ezetimibe to simvastatin was translated into 8.8% (95% CI: 3.1 to 14.6) absolute risk reduction in patients with previous CABG compared to merely 1.3% (95% CI: 0 to 2.6%) in those patients without previous CABG history[29]. Moreover, a recent meta-analysis revealed the incremental benefits of intensive lipid lowering therapy in patients post CABG[30]. Remarkably, there was a significant 14% reduction in all-cause mortality [rate ratio (RR) 0.86; (95% CI, 0.74 to 0.99)] and 25% reduction in cardiovascular mortality [RR 0.75; (95% CI, 0.65 to 0.86)] when subjected patients post CABG to intensive lipid lowering therapy[30]. Unpublished data suggest that the mortality benefit in patients post CABG was independent of the level of baseline LDL-c. In other words, patients post CABG with LDL-c > 100 mg/dL sustained 2.5% (95% CI: 0 to 4.8%) absolute risk reduction compared to 1.2% (95% CI: -1.0 to 3.5) in patients without previous CABG.

The heightened risk in patient post CABG warrants consideration of early introduction of intensive lipid-lowering therapy, particularly since the benefits were not merely related to a composite clinical endpoint but was extended to include all-cause and cardiovascular mortality. Importantly, the level of LDL-c does not determine the efficacy of intensive lipid-lowering therapy and whether upfront and targeted approach for this group would be an alternative option in a cost-effective, sustainable platform in most health care systems needs to be explored.

PATIENTS WITH DIABETES AND METABOLIC SYNDROME

Patients with diabetes mellitus are at increased risk of future cardiovascular events[31-34]. The aggressive nature and extent of atherosclerosis burden, despite glucose normalisation, is recognised as a potential mechanism of this increased risk[31-34]. Statin is recommended in this group for primary and secondary prevention[2]. Notably, statin treatment is associated with 0.5-1.0% increase in the incidence of new-onset diabetes[24]. Similarly, certain variants in PCSK9 genes were also reported to increase the risk of diabetes. Data suggest that there is 10% increase in the risk of diabetes for each 10 mg/dL reduction in LDL-c[9,35]. Nonetheless, pharmacological inhibition of PCSK9 was not associated with an increase in the incidence of diabetes.
Abdalwahab A et al. Lipid lowering therapy beyond LDL-c

mellitus, nor affect glycaemic control[36-38]. Moreover, in a large meta-analysis of 33 randomized trials including 163688 non-diabetic patients, PCSK9 inhibitors were not associated with new onset diabetes[39].

In the IMPROVE-IT and ODYSSEY Outcomes trials, intensive lipid-lowering therapies using ezetimibe and alirocumab, respectively, lowered LDL-c compared to placebo, irrespective of the diabetic status of patients[37,40]. Nevertheless, the absolute risk reduction using ezetimibe was 5.5% in diabetic patients, which was significantly larger compared to 0.7% in non-diabetic patients (\(P = 0.002\) for interaction)[40]. Likewise, in response to intensive LDL-c reduction using PCSK9 inhibitors, the absolute reduction in adverse cardiovascular events in diabetic patients (2.3%, 95%CI 0.4 to 4.2) was better than in those with prediabetes (1.2%, 95%CI: 0.0 to 2.4) or normoglycaemia (1.2%, 95%CI: -0.3 to 2.7) (\(P = 0.0019\) for interaction)[37]. Similarly, evolocumab in the FOURIER trial showed more absolute risk reduction in the primary end point in diabetic vs non-diabetic groups [(2.7%; 95%CI: 0.7 to 4.8) and (1.6%; 95%CI, 0.1 to 3.2)][38]. Interestingly, the reduction in atherosclerosis burden on intravascular ultrasound (IVUS) was comparable between diabetic and non-diabetic in response to PCSK9 inhibition[10].

Patients with metabolic syndrome are at increased risks of developing diabetes and cardiovascular disease[41]. It is characterised as a cluster of conditions including central obesity, insulin resistance, hypertension and dyslipidaemia. Metabolic syndrome is common and was reported in almost 60% of recruited patients in the FOURIER trial, and more importantly, was associated with 30% increase in the risk of future adverse cardiovascular events[42]. Evolocumab was associated with similar LDL-c reduction, irrespective of the status of metabolic syndrome[42]. Moreover, it reduced cardiovascular events by 17% in this subgroup HR 0.83 95%CI: 0.76 to 0.91[42].

**ELDERLY PATIENTS**

Old age is a risk for adverse cardiovascular events and most individuals aged 65 or above are already at high or very high risk[43]. Elderly population are under-represented in clinical trials and the recent CTTC reported that previous statin trials included only 8% of patients > 75[44]. Moreover, side effects, co-morbidities, and interactions with other medications add more challenges to intensive lipid-lowering therapy in the elderly. Nonetheless, LDL-c reduction using statin was associated with 21% proportionate reduction in major vascular events in the elderly[44]. There was a trend towards diminishing efficacy with increased age, although this did not reach statistical significance[44].

In a pre-specified secondary analysis of the IMPROVE-IT trial, Bach et al[45] reported 8.7% absolute risk reduction when adding ezetimibe to simvastatin in elderly patients (> 75 years). In comparison, for patients below 65 years and between 65-74 years, their absolute risk reduction was 0.9% and 0.8%, respectively. Similar findings were reported from the ODYSSEY Outcomes trial, whereby alirocumab was associated with larger absolute risk reduction with increasing age: 2.3% at age 45; 3.8% at age 75; and 8.3% at age 85 years[46]. Interestingly, data from the FOURIER trial suggest small variations in the incidence of major vascular events according to age groups with a consistent finding that evolocumab reduced adverse events regardless of patient age[47]. Similarly, in the ODYSSEY OUTCOMES trial age did not appear to modify the beneficial effects of LDL-c lowering using PCSK9 inhibitors[7]. In contrast, the relative risk reduction associated with ezetimibe was only evident in the group of patients > 75 years (HR, 0.80; 95%CI, 0.70-0.90) while the other groups had relative risk reduction of less than 5% (\(P = 0.02\) for interaction). Notably, the difference in LDL-c reduction was comparable across the age groups.

This apparent inconsistency in the impact of intensive lipid lowering across age in different studies should not be surprising. In fact, this phenomenon could possibly be extended to other “high risk” clinical features (Table 1). The mechanism by which lipid-lowering therapy exerts clinical benefit is by evacuating lipid from atherosclerotic plaque, rendering them more stable[5,48]. Therefore, patients with large burden of atherosclerotic plaque or more specifically lipid rich plaque are likely to benefit more from intensive lipid lowering therapy. In other words, the largest absolute risk reduction is anticipated in the highest risk group and the benefit should be proportionate to the baseline absolute risk. However, this is only true if the residual risk is homogeneous and if the applied therapy targets that specific risk[1,5,9]. However, in elderly populations the residual risk is heterogeneous, and intensive lipid
Table 1 Cardiovascular outcome of proprotein convertase subtilisin kexin 9 inhibitors vs Placebo in different studies and subgroups

| Patients with Polyvascular disease | Alirocumab vs placebo |
|-----------------------------------|------------------------|
| Monovascular (n = 17370)          | Cardiovascular events: ARR 1.4% (CI 95%; 0.6%-2.3%) | Mortality: 0.4% (95%CI: -0.1% to 1.0%) |
| 2 vascular beds (n = 1405)        | Cardiovascular events: ARR 1.9% (CI 95%; -2.4%-6.2%) | Mortality: ARR 1.3% (95%CI: -1.8% to 4.3%) |
| 3 vascular beds (n = 149)         | Cardiovascular events: ARR 13% (CI 95%; -2%-28%) | Mortality: ARR 16.2% (95%CI: 5.5% to 26.8%) |

FOURIER Trial (n = 27564)            | Evolocumab vs placebo |
|-------------------------------------|------------------------|
| With PAD (n = 2642)                 | Composite of major cardiac events ARR 3.5% HR 0.79; 95%CI, 0.66-0.94; P = 0.0098 |
| Without PAD (n = 24922)             | Composite of major cardiac events ARR: 1.6% HR 0.86; 95%CI, 0.80-0.93; P = 0.0003 |

Patients with prior CABG

| ODYSEY trial subgroup (n = 18924) | Alirocumab vs placebo |
|-----------------------------------|------------------------|
| With Prior CABG (n = 1003)        | Composite of major cardiac events ARR: 6.4%; 95%CI: 0.9 to 12.0 |
| With index CABG (n = 1025)        | Composite of major cardiac events ARR: 0.9%; 95%CI: 2.3 to 4.0 |
| Without prior CABG (n = 16896)    | Composite of major cardiac events ARR: 1.3%; 95%CI: 0.5 to 2.2 |

Patients with diabetes mellitus or metabolic syndrome

| FOURIER Trial diabetic subgroup (n = 27564) | Evolocumab vs placebo |
|---------------------------------------------|------------------------|
| With diabetes (n = 11031)                   | Composite of major cardiac events HR 0.83 (95%CI 0.75-0.93; P = 0.0008), Absolute risk reduction 2.7% (95%CI 0.7-4.8) |
| Without diabetes (n = 16533)               | Composite of major cardiac events HR 0.87 (0.79-0.96; P = 0.0052)Absolute risk reduction 1.6% (95%CI 0.1-3.2) |

FOURIER trial metabolic syndrome subgroup (n = 27342) | Evolocumab vs placebo |

| With met syndrome (n = 16361) | Composite of major cardiac events HR 0.83 (95%CI; 0.76-0.91) |
| Without met syndrome (n = 10981) | Composite of major cardiac events HR 0.89, CI 95% (0.79-1.01) |

ODYSSEY trial subgroup (n = 18924) | Alirocumab vs placebo |
|-----------------------------------|------------------------|
| With diabetic (n = 5444)          | Composite of major cardiac events ARR 2.3%, 95%CI 0.4 to 4.2 |
| Prediabetic (n = 8246)            | Composite of major cardiac events ARR 1.2%, 95%CI: 0.0 to 2.4 |
| Normoglycemic (n = 5234)          | Composite of major cardiac events ARR 1.2%, 95%CI: −0.3 to 2.7 |

Elderly patients

| FOURIER trial (n = 27564) age subgroup[49] | Evolocumab vs placebo |
|---------------------------------------------|------------------------|
| Q1                                           | Composite of major cardiac events HR 0.83, 95%CI 0.72-0.96 |
| Q2                                           | Composite of major cardiac events HR 0.88, 95%CI 0.76-1.01 |
| Q3                                           | Composite of major cardiac events HR 0.82, 95%CI 0.71-0.95 |
| Q4                                           | Composite of major cardiac events HR 0.86, 95%CI 0.74-1.00 |

ODYSSEY trial age subgroup (n = 18924) | Alirocumab vs placebo |
|--------------------------------------|------------------------|
| ≥ 65 yr                               | Composite of major cardiac events HR 0.78, 95%CI 0.68-0.91 |
| < 65 yr                               | Composite of major cardiac events HR 0.89, 95%CI 0.80-1.00 |

lowering therapies were applied unselectively without measures of atherosclerosis disease burden. Recent developments have allowed in-vivo plaque imaging and lipid quantification to aid decision making in using intensive lipid lowering drug[49-51].

ROLE OF PLAQUE IMAGING TO GUIDE INTENSIVE LIPID-LOWERING TREATMENTS

The lipoprotein-related risk is heterogeneous and likely to be related to other non-LDL-c parameters. As highlighted above the use of LDL-c in the post statin era could
be challenged as the magnitude of LDL-c reduction did not reflect clinical outcomes in patients using intensive lipid lowering therapy. High-density lipoprotein (HDL-c) was highlighted as a prognostic marker with an inverse relationship with adverse outcomes in patients with cardiovascular disease[52]. Nonetheless, it failed as a therapeutic target with no effect on cardiovascular outcomes despite significant increase in HDL-c levels using niacin and cholesterol-ester transfer protein inhibitors [53-55]. Recent data suggest that the level of triglyceride and remnant cholesterol are associated with cardiovascular outcomes, independent of other risk factors, including LDL-c[56]. Moreover, VLDL-c was associated with double the hazard of myocardial infarction in the Copenhagen General Population Study which included more than 100,000 individuals[57]. Targeted therapies are in development to assess whether certain lipid biomarkers, such as Lp(a), could be used as therapeutic target, in addition to LDL-c[58]. This approach is promising as certain markers such as lipoprotein (a) would identify high risk patients and, therefore, targeting this particular biomarker maybe associated with a reduction in future cardiovascular events.

Overall, the complex interaction between lipid biomarkers would render a single marker imprecise in predicting clinical outcomes. Collectively, these markers target atherosclerotic plaque progression or regression, and therefore, characterising plaque would provide a better and more comprehensive picture on future plaque, and patient risk. Invasive and non-invasive imaging tools, such as near infra-red spectroscopy and T2 mapping, would allow precise measurement and characterisation of lipid core within atherosclerotic plaque. Patients with propensity to develop lipid-rich plaque may be suitable candidate for intensive lipid-lowering drug. Remarkably, clinical entities that demonstrate large improvement in clinical outcomes shared similar profile in the atherosclerotic disease process. Patients with polyvascular disease, post CABG and diabetes are reported to have advanced and aggressive atherosclerotic disease and, therefore, intensive lipid lowering therapy had produced mortality benefits in certain cases. The use of plaque imaging may risk stratify patients and provide a platform to monitor patients response to lipid-lowering therapy. Patients with large lipid-rich plaques in multiple vascular territories or those who have poor or suboptimal response to statin, may be suitable candidates for more expensive therapies. These treatments would be rationalised according to the atherosclerotic disease characteristics and not merely based on a single marker that is unlikely to reflect patient future risk. Future randomised clinical trials are needed to assess whether the proposed approach would prove to be cost-effective. The use of atherosclerotic disease characteristics to guide decision making for intensive, yet, expensive lipid-lowering therapy is a step toward more personalised and precision medicine.

**CONCLUSION**

LDL-c plays an important role in the development of atherosclerotic disease as evidenced by the proportionate reduction in LDL-c improving cardiovascular outcomes with statin use. Nevertheless, the heterogeneous residual risk post statin challenges the use of LDL-c as a single maker to guide additional lipid lowering therapy. Emerging data suggest that patients with large atherosclerotic burden appear to sustain increased benefits from intensive lipid-lowering therapy. Future studies are in development to assess whether plaque imaging and phenotypic features associated with larger atherosclerotic burden would help identify patients who may benefit from additional intensive lipid lowering treatments.

**REFERENCES**

1. Alkhalil M. Mechanistic Insights to Target Atherosclerosis Residual Risk. *Curr Probl Cardiol* 2021; 46:100432 [PMID: 31285037 DOI: 10.1016/j.cpcardiol.2019.06.004]

2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41:111-188 [PMID: 31054418 DOI: 10.1093/eurheartj/ehz455]

3. Cholesterol Treatment Trials’ (CTT) Collaboration. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in
26 randomised trials. *Lancet* 2010; 376: 1670-1681 [PMID: 21067804 DOI: 10.1016/S0140-6736(10)61350-5]

4 Jarcho JA, Keaney JF Jr. Proof That Lower Is Better--LDL Cholesterol and IMPROVE-IT. *N Engl J Med* 2015; 372: 2448-2450 [PMID: 26039520 DOI: 10.1056/NEJMct1507041]

5 Alkhaili M, Chai JT, Choudhury RP. Plaque imaging to refine indications for emerging lipid-lowering drugs. *Eur Heart J Cardiovasc Pharmacother* 2017; 3: 58-67 [PMID: 27816944 DOI: 10.1093/ehjcvp/pxv034]

6 Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JD, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferranti GM, Ruzzillo W, De Luca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; 372: 2387-2397 [PMID: 26039525 DOI: 10.1056/NEJMoa1410489]

7 Schwartz GG, Steg PG, Sarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379: 2097-2107 [PMID: 30403574 DOI: 10.1056/NEJMoa1801174]

8 Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somarantne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; 372: 1500-1509 [PMID: 25773607 DOI: 10.1056/NEJMoa1500858]

9 Alkhaili M. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors, Reality or Dream in Managing Patients with Cardiovascular Disease. *Curr Drug Metab* 2019; 20: 72-82 [PMID: 31029987 DOI: 10.2174/138920021966618016141827]

10 Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Chico L, Kastelein JJ, Koenig W, Somarantne R, Kassahun H, Yang J, Wasserman SM, Scott R, Unni I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* 2016; 319: 2373-2384 [PMID: 27846344 DOI: 10.1001/jama.2016.16951]

11 Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Blien K, Tantry U, Kubica J, Raggi P, Gurbel PA. Association Between Baseline LDL-C Level and Total and Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. *JAMA* 2018; 319: 1566-1579 [PMID: 29677301 DOI: 10.1001/jama.2018.2525]

12 Hoogeveen RC, Ballantyne CM. Residual Cardiovascular Risk at Low LDL: Remnants, Lipoprotein(a), and Inflammation. *Clin Chem* 2021; 67: 143-153 [PMID: 33257928 DOI: 10.1093/clinchem/hva252]

13 Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. *JAMA* 2017; 318: 748-750 [PMID: 28529663 DOI: 10.1001/jama.2017.9924]

14 Hlatky MA, Kazi DS. PCSK9 Inhibitors: Economics and Policy. *J Am Coll Cardiol* 2017; 70: 2677-2687 [PMID: 29169476 DOI: 10.1016/j.jacl.2017.10.001]

15 Lipid-modifying drugs. NICE guidance. Available from: https://www.nice.org.uk/advice/kn3/chapter/evidence-context#alirocumab-and-evolocumab

16 Gutierrez JA, Aday AW, Patel MR, Jones WS. Polyvascular Disease: Reappraisal of the Current Clinical Landscape. *Circ Cardiovasc Interv* 2019; 12: e007385 [PMID: 31833412 DOI: 10.1161/CIRCINTERVENTIONS.119.007385]

17 Dikilitas O, Satterfield BA, Kullo IJ. Risk Factors for Polyvascular Involvement in Patients With Peripheral Artery Disease: A Mendelian Randomization Study. *J Am Heart Assoc* 2020; 9: e017740 [PMID: 33287626 DOI: 10.1161/JAHA.120.017740]

18 Ommen EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS, Mas JL, Richard AJ, Röther J, Wilson PW; REACH Registry Investigators. The REDuction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J* 2006; 151: 786.e1-786.10 [PMID: 16595533 DOI: 10.1016/j.ahj.2005.11.004]

19 Bonaca MP, Gutierrez JA, Cannon C, Giugliano R, Blazing M, Park JG, White JA, Tershakovec A, Braunwald E. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol* 2018; 6: 934-943 [PMID: 30396865 DOI: 10.1016/S2213-8587(18)30290-0]

20 Landmesser U, Chapman MJ, Stock JK, Amarenco P, Belch JF, Borén J, Farnier M, Ference BA, Gielen S, Graham I, Grobbée DE, Hovingh GK, Lüscher TF, Piepoli MF, Ray KK, Stroes ES, Wiklund O, Windecker S, Zannorano JL, Pinto F, Tokgözoglu L, Bax JJ, Catapano AL. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J* 2018; 39: 1131-1143 [PMID: 29045644 DOI: 10.1093/eurheartj/ehx549]

21 Jukema JW, Sarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Karpov Y, Moryusef A, Pordy R, Prieto JC, Roe MT, White HD, Zeiher AM, Schwartz GG, Steg PG; ODYSSEY OUTCOMES Committees and Investigators.
Abdalwahab A et al. Lipid lowering therapy beyond LDL-c

Investigators. Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. J Am Coll Cardiol 2019; 74: 1167-1176 [PMID: 30898609 DOI: 10.1016/j.jacc.2019.03.013]

22 Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanekovsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 2018; 137: 338-350 [PMID: 29213605 DOI: 10.1161/CIRCULATIONAHA.117.032235]

23 Alkhali M, Kuzemczak M, Whitehead N, Kavvouras C, Džavík V. Meta-Analysis of Intensive Lipid-Lowering Therapy in Patients With Polyvascular Disease. J Am Heart Assoc 2021; 10: e017948 [PMID: 33586467 DOI: 10.1161/JAHA.120.017948]

24 Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Petro R. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388: 2532-2561 [PMID: 27616593 DOI: 10.1016/S0140-6736(16)31357-5]

25 Creen PA, Waters DD, Bosch X, Pelletier GB, Roy D, Théroux P. Angiographic findings after myocardial infarction in patients with previous bypass surgery: explanations for smaller infarcts in this group compared with control patients. Circulation 1985; 71: 693-698 [PMID: 3871669 DOI: 10.1161/01.CIR.71.4.693]

26 Fitzgibbons GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996; 28: 616-626 [PMID: 8772748 DOI: 10.1016/0735-1097(96)00206-9]

27 Knatterud GL, Rosenberg Y, Campeau L, Geller NL, Hunninghake DB, Foraman SA, Forrester JS, Gobel FL, Herd JA, Hickey A, Hoogwerf BJ, Terrin ML, White C. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Post CABG Investigators. Circulation 2000; 102: 157-165 [PMID: 10889125 DOI: 10.1161/01.CIR.102.2.157]

28 Goodman SG, Aylward PE, Szarek M, Chamburidze V, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Hanotin C, Harrington RA, Jukema JW, Kedev S, Letierce A, Moryusef A, Pordy R, Ramos Lopez GA, Roe MT, Vignuama M, White HD, Zeiher AM, Steg PG, Schwartz GG; ODYSSEY OUTCOMES Committees and Investigators. Effects of Alirocumab on Cardiovascular Events After Coronary Bypass Surgery. J Am Coll Cardiol 2019; 74: 1177-1186 [PMID: 31466614 DOI: 10.1016/j.jacc.2019.07.012]

29 Eisen A, Cannon CP, Blazing MA, Bohula EA, Park JG, Murin J, Moryusef A, Pordy R, Ramos Lopez GA, Roe MT, Vignuama M, White HD, Zeiher AM, Steg PG, Schwartz GG; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndromes: A Prespecified Analysis of ODYSSEY OUTCOMES. Circulation 2020; 141: 2756-2774 [PMID: 32605641 DOI: 10.1161/CIRCULATIONAHA.120.043663]

30 Alkhali M. Effects of intensive lipid-lowering therapy on mortality after coronary bypass surgery: A meta-analysis of 7 randomised trials. Atherosclerosis 2020; 293: 73-78 [PMID: 31865057 DOI: 10.1016/atherosclerosis.2019.12.006]

31 Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCaren M, Duckworth WC, Hayward RA; VADT Investigators. Intensive Glucose Control in Patients With Type 2 Diabetes - 15-Year Follow-up. N Engl J Med 2019; 380: 2215-2224 [PMID: 31167051 DOI: 10.1056/NEJMoa1806802]

32 Parathath S, Grauer L, Huang LS, Sanson M, Distel E, Goldberg IJ, Fisher EA. Diabetes adversely affects macrophages during atherosclerotic plaque regression in mice. Diabetes 2011; 60: 1759-1769 [PMID: 21562077 DOI: 10.2337/db10-0778]

33 Shannumag N, Reddy MA, Guha M, Natarajan R. High glucose-induced expression of proinflammatory cytokine and chemokine genes in mononcyclic cells. Diabetes 2003; 52: 1256-1264 [PMID: 12716761 DOI: 10.2337/diabetes.52.5.1256]

34 Goraya TV, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, Jacobsen SJ, Frye RL, Roger VL. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. J Am Coll Cardiol 2002; 40: 946-953 [PMID: 12225721 DOI: 10.1016/S0735-1097(02)02065-x]

35 Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. N Engl J Med 2016; 375: 2144-2153 [PMID: 27095767 DOI: 10.1056/NEJMoa1604304]

36 Monami M, Sesti G, Mannucci E. PCSK9 inhibitor therapy: A systematic review and meta-analysis of metabolic and cardiovascular outcomes in patients with diabetes. Diabetes Obes Metab 2019; 21: 903-908 [PMID: 30485622 DOI: 10.1111/dom.13599]

37 Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, Budaj AJ, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Loizeau V, Lopes RD, Moryusef A, Murin J, Pordy R, Ristic AD, Roe MT, Tufano J, White HD, Zeiher AM, Schwartz GG; Steg PG; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis
of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019; 7: 618-628 [PMID: 31272931 DOI: 10.1016/S2213-8587(19)30158-5]

38 Sabatine MS, Leiter LA, Vlixioti SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; 5: 941-950 [PMID: 28927706 DOI: 10.1016/S2213-8587(17)30313-3]

39 Khan SU, Rahman H, Okunrintemi V, Riaz H, Khan MS, Sattar S, Kaluski E, Lincoff AM, Martin SS, Blaha MJ. Association of Lowering Low-Density Lipoprotein Cholesterol With Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019; 8: e011581 [PMID: 30898075 DOI: 10.1161/JAHA.118.011581]

40 Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špiran J, Park JG, White JA, Bohula EA, Braunwald E; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018; 137: 1571-1582 [PMID: 29263150 DOI: 10.1161/CIRCULATIONAHA.117.030950]

41 Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis* 2017; 11: 215-225 [PMID: 28639538 DOI: 10.1177/1759373417711379]

42 Deedwania P, Murphy SA, Scheen A, Badarini E, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR, Sabatine MS, Giugliano RP. Efficacy and Safety of PCSK9 Inhibition With Evolocumab in Reducing Cardiovascular Events in Patients With Metabolic Syndrome Receiving Statin Therapy: Secondary Analysis From the FOURIER Randomised Controlled Trial. *JAMA Cardiol* 2021; 6: 139-147 [PMID: 32785614 DOI: 10.1001/jamacardio.2020.3151]

43 Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Lölgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Di S, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; 37: 2315-2381 [PMID: 27222591 DOI: 10.1093/eurheartj/ehw106]

44 Cholesterol Treatment Trialists’ Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019; 393: 407-415 [PMID: 30712900 DOI: 10.1016/S0140-6736(18)31942-1]

45 Bach RG, Cannon CP, Giugliano RP, White JA, Lokhnygina Y, Bohula EA, Calif rm SS, Braunwald E, Blazing MA. Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol* 2019; 4: 846-854 [PMID: 31340500 DOI: 10.1001/jamacardio.2019.2360]

46 Sinnaeve PR, Schwartz GG, Wijdtya DM, Alings M, Bhatt DL, Bittner VA, Chiang CE, Correa Flores RM, Diaz R, Dorobantu M, Goodman SG, Jukema JW, Kim YU, Pondy R, Roe MT, Sy RG, Szarek M, White HD, Zeiher AM, Steg PG; ODYSSEY OUTCOMES Investigators. Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis. *Eur Heart J* 2020; 41: 2248-2258 [PMID: 31732742 DOI: 10.1093/eurheartj/ehz809]

47 Sever P, Gouni-Berthold I, Kech K, Giugliano R, Pedersen TR, Im K, Wang H, Knusel B, Sabatine MS, O'Donoghue ML. LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial. *J Eur Prev Cardiol* 2020; 204748320902750 [PMID: 32019364 DOI: 10.1177/204748320902750]

48 Alkhalil M, Biasiolli L, Akbar N, Galassi F, Chai JT, Robson MD, Choudhary RP. T2 mapping MRI technique quantifies carotid plaque lipid, and its depletion after statin initiation, following acute myocardial infarction. *Atherosclerosis* 2018; 279: 100-106 [PMID: 30227940 DOI: 10.1016/j.atherosclerosis.2018.08.033]

49 Waksman R, Di Mario C, Torsogus R, Ali ZA, Singh V, Skinner WH, Artis AK, Cate TT, Powers E, Kim C, Regar E, Wong SC, Lewis S, Wykrzykowska J, Dame S, Kazzhia S, van der Ent M, Shah P, Craig PE, Zou Q, Kolm P, Brewer HB, Garcia-Garcia HM; LRP Investigators. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet* 2019; 394: 1629-1637 [PMID: 31570255 DOI: 10.1016/S0140-6736(19)31794-5]

50 Negi SI, Didier R, Ota H, Magalhaes MA, Popma CJ, Koller MR, Spad MA, Torguson R, Suddath W, Satler LF, Richard A, Waksman R. Role of near-infrared spectroscopy in intravascular coronary imaging. *Cardiovasc Revasc Med* 2015; 16: 299-305 [PMID: 26242984 DOI: 10.1016/j.carrev.2015.06.001]

51 Alkhalil M, Biasiolli L, Chai JT, Galassi F, Li L, Darby C, Halliday A, Hands L, Magee T, Perkins J, Sidese E, Jeard P, Robson MD, Handa A, Choudhry RP. Quantification of carotid plaque lipid
content with magnetic resonance T2 mapping in patients undergoing carotid endarterectomy. *PLoS One* 2017; 12: e0181668 [PMID: 28746385 DOI: 10.1371/journal.pone.0181668]

52 Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 1977; 62: 707-714 [PMID: 193398 DOI: 10.1016/0002-9343(77)90874-9]

53 AIM-HIGH Investigators. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365: 2255-2267 [PMID: 22085343 DOI: 10.1056/NEJMoa1107579]

54 Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, Gibson CM, Granger C, Menon V, Montalescot G, Rader D, Tall AR, McErlean E, Wolski K, Ruotolo G, Vangerow B, Weerakkody G, Goodman SG, Conde D, McGuire DK, Nicolau JC, Leiva-Pons JL, Pesant Y, Li W, Kandath D, Kozz S, Tahirkheli N, Mason D, Nissen SE; ACCELERATE Investigators. Evaacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* 2017; 376: 1933-1942 [PMID: 28514624 DOI: 10.1056/NEJMoa1609581]

55 Schwartz GG, Olsson AG, Abd M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OCTOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 367: 2089-2099 [PMID: 23126252 DOI: 10.1056/NEJMoa1206797]

56 Castañer O, Pintó X, Subirana I, Amor AJ, Ros E, Hernández Á, Martínez-González MÁ, Corella D, Salas-Salvadó J, Estruch R, Lapetra J, Gómez-Gracia E, Alonso-Gomez AM, Fiôl M, Serra-Majem L, Corbella E, Benaiges D, Sorlí JV, Ruiz-Canela M, Bahló N, Sierra LT, Ortega E, Fitó M. Remnant Cholesterol, Not HDL Cholesterol, Is Associated With Incident Cardiovascular Disease. *J Am Coll Cardiol* 2020; 76: 2712-2724 [PMID: 33272365 DOI: 10.1016/j.jacc.2020.10.008]

57 Balling M, Afzal S, Varbo A, Langsted A, Davey Smith G, Nordestgaard BG. VLDL Cholesterol Accounts for One-Half of the Risk of Myocardial Infarction Associated With apoB-Containing Lipoproteins. *J Am Coll Cardiol* 2020; 76: 2725-2735 [PMID: 33272366 DOI: 10.1016/j.jacc.2020.09.610]

58 Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, Shapiro MD, Stroes ES, Moriarty PM, Nordestgaard BG, Xia S, Guerriero J, Viney NJ, O’Dea L, Witztum JL; AKCEA-APO(a)-LRx Study Investigators. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *N Engl J Med* 2020; 382: 244-255 [PMID: 31893580 DOI: 10.1056/NEJMoa1905239]
