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REVIEW

- 381 Quantifying tissue perfusion after peripheral endovascular procedures: Novel tissue perfusion endpoints to improve outcomes
Arkoudis NA, Katsanos K, Inchingolo R, Paraskevopoulos I, Mariappan M, Spiliopoulos S
- 399 Exercise-mediated adaptations in vascular function and structure: Beneficial effects in coronary artery disease
Sakellariou XM, Papafaklis MI, Domouzoglou EM, Katsouras CS, Michalis LK, Naka KK
- 416 Stent visualization methods to guide percutaneous coronary interventions and assess long-term patency
Ghafari C, Carlier S

MINIREVIEWS

- 438 Interpersonal violence: Serious sequelae for heart disease in women
Mazza M, Marano G, Gonzalez del Castillo A, Chieffo D, Albano G, Biondi-Zoccai G, Galiuto L, Sani G, Romagnoli E
- 446 Coronary artery aneurysm: A review
Matta AG, Yaacoub N, Nader V, Moussallem N, Carrie D, Roncalli J
- 456 Coronary vasospasm: A narrative review
Jewulski J, Khanal S, Dahal K
- 464 Sodium glucose cotransporter 2 inhibitors: New horizon of the heart failure pharmacotherapy
Naito R, Kasai T
- 472 Intensive lipid-lowering therapy, time to think beyond low-density lipoprotein cholesterol
Abdalwahab A, Al-atta A, Zaman A, Alkhalil M

ORIGINAL ARTICLE**Retrospective Study**

- 483 Patients' time in therapeutic range on warfarin among atrial fibrillation patients in Warfarin Medication Therapy Adherence Clinic
Lee SL, Ong TJ, Mazlan-Kepli W, Mageswaran A, Tan KH, Abd-Malek AM, Cronshaw R
- 493 Percutaneous coronary intervention of totally occluded coronary venous bypass grafts: An exercise in futility?
Nardone EW, Madsen BM, McCarey MM, Fischman DL, Ruggiero NJ, Walinsky P, Vishnevsky A, Savage MP

Prospective Study

- 503 Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease
Xanthopoulos A, Tryposkiadis K, Dimos A, Bourazana A, Zagouras A, Iakovis N, Papamichalis M, Giamouzis G, Vassilopoulos G, Skoularigis J, Triposkiadis F
- 514 Effects of exercise training on diastolic and systolic dysfunction in patients with chronic heart failure
Chaveles I, Papazachou O, Shamari MA, Delis D, Ntalianis A, Panagopoulou N, Nanas S, Karatzanos E

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

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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

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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.

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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 169138 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[5,9]. 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, may be 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 \geq 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, 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, Alkhalil *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 CTC 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, alirocumab 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 subjecting 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

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

ODYSSEY trial subgroup (n = 18924)	Alirocumab vs placebo
<i>Patients with Polyvascular disease</i>	
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
<i>Patients with prior CABG</i>	
ODYSSEY 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
<i>Patients with diabetes mellitus or metabolic syndrome</i>	
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
<i>Elderly patients</i>	
FOURIER trial (n = 27564) age subgroup[8]	
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 100000 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 may be 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.

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