Novel targets and strategies addressing residual cardiovascular risk in post-acute coronary syndromes patients

Francesco Paolo Cancro
Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

Michele Bellino
Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

Angelo Silverio
Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

Marco Di Maio
Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

Luca Esposito
Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

See next page for additional authors

Follow this and additional works at: https://tmj.unisa.it/journal

Part of the Health Communication Commons, Life Sciences Commons, and the Medicine and Health Sciences Commons

Novel targets and strategies addressing residual cardiovascular risk in post-acute coronary syndromes patients

Authors

Francesco Paolo Cancro, Michele Bellino, Angelo Silverio, Marco Di Maio, Luca Esposito, Rossana Palumbo, Martina La Manna, Ciro Formisano, Germano Ferruzzi, Carmine Vecchione, and Gennaro Galasso

REVIEW

Novel Targets and Strategies Addressing Residual Cardiovascular Risk in Post-acute Coronary Syndromes Patients

Francesco P. Cancro, Michele Bellino[*], Angelo Silverio, Marco Di Maio, Luca Esposito, Rossana Palumbo, Martina L. Manna, Ciro Formisano, Germano Ferruzzi, Carmine Vecchione, Gennaro Galasso

Department of Medicine Surgery and Dentistry, University of Salerno, Baronissi, SA, Italy

Abstract

Despite the advancement in secondary cardiovascular prevention strategies for post-acute coronary syndrome (ACS) patients, the development of new drugs addressing dyslipidemia and the personalization of dual antiplatelet therapies (DAPT), these patients continue to suffer a significant incidence of recurrent ischemic events. Therefore, novel targets that can be tackled to reduce cardiovascular risk are needed to improve the outcome of this very high-risk population.

The role of chronic inflammation and inflammasome in the development and progression of atherosclerosis has been broadly investigated in patients with established coronary artery disease (CAD) and recent randomized trials have highlighted the possibility to manage these targets with specific drugs such as colchicine and monocolonal antibodies with a significant improvement of cardiovascular outcomes in post-ACS patients.

Lipoprotein(a) [Lp(a)] is the most promising non-traditional risk factor and has shown to predict worse outcome in post-ACS patients. Lowering Lp(a) through PCSK9 inhibitors and specific targeted therapies has shown positive results in reducing adverse cardiovascular events in patients with established CAD.

The effect of microbiome and its alteration in gut dysbiosis seems to actively participate in residual cardiovascular risk of CAD patients; however, the risk-modifying effect of targeted-microbiome therapies hasn't been yet investigated in large population-based studies.

Long-term outcome of post-ACS patients is a complex puzzle of multiple factors.

In this minireview, we summarize the emerging risk factors that may interplay in the residual risk of post-ACS patients and their possible prognostic and therapeutic implications.

Keywords: Acute coronary syndrome, Secondary prevention, Coronary artery disease, Lipoprotein(a), Inflammation, Inflammasome, Microbiota, Emerging therapies

1. Introduction

Despite continuous advancement in primary and secondary prevention strategies [1–3], improved percutaneous coronary intervention (PCI) techniques [4–6], patients with previous myocardial infarction (MI) continue to experience a significant number of recurrent ischemic events [7–10].

That said, the necessity of targeted intervention in this population raises in order to lower their residual cardiovascular risk, despite optimal guideline-guided therapy [11].

It is clear that mere control of traditional risk factors and lifestyle is not enough to effectively minimize the residual risk of these patients. Therefore, a tailored approach directed at detecting and

treating novel and additional risk factors is required to achieve improved short- and long-term prognosis after an Acute Coronary Syndrome (ACS) [12–16].

The purpose of this mini-review is to summarize the underlying pathophysiological mechanisms of residual cardiovascular risk in post-ACS patients, to outline new risk factors associated with recurrent ischemic events, and to suggest new potential therapeutic targets that may be considered in this very high-risk population (Fig. 1).

2. Residual cardiovascular risk after ACS and the limitations of traditional risk factors

In recent years it has become clear that the underlying pathophysiological pathway of ACS is a complex puzzle involving a multitude of elements that leads to the instabilization of atherosclerotic plaque, and the exposure of prothrombotic elements that enhance thrombus formation with the consequential obstruction of the coronary arteries and the development of ACS. This process appears complex since it has been observed in several cases that significantly flow-limiting stable plaques show signs of multiple cycles of rupture and self-healing [17,18]. This assumption has also been corroborated by intravascular imaging studies that have described how morphologically vulnerable plaques could, according to a not yet fully elucidated mechanism, progress to a stable condition, presumably through cycles of rupture and spontaneous healing [19,20]. On the other hand, in some patients, the prothrombotic mechanism outweighs the healing process resulting in the evolution toward an ACS. In these patients, there could be a pathophysiological

predisposition that makes them more susceptible to the occurrence of ischemic events. Moreover, this hypothesis has been supported by several clinical studies in which was observed that post-ACS patients had a significantly higher risk of ischemic events than patients with stable CAD, who have not experienced previous ACS [21,22].

Furthermore, the recurrence of ischemic events in post-ACS patients is reported between 4.4% and 6.7%, with an increased risk in the first 12 months post-ACS and a steady increase even in the long term [8,23,24]. These findings reveal how, despite optimal invasive and pharmacological treatments, a significant residual risk persists in this cohort of patients.

The management of residual cardiovascular risk of post-ACS patients needs to consider a complex network of factors. Exogenous factors such as lifestyle habits, diet, daily activities, and biomolecular factors such as thrombotic activity, lipoproteins, and inflammation all intersect and interact with each other. In recent decades, research efforts have focused on reducing thrombotic events with interventions aimed at preventing the instabilization of atherosclerotic plaques through the development of increasingly effective hypolipidemic drugs [25], as well as directly targeting thrombotic activity with the use of antiplatelet drugs and dual antiplatelet therapy (DAPT). The latter, represents the cornerstone of pharmacological therapy in post-ACS, and in recent years DAPT strategies have been adjusted to fit particular cohorts of patients with prohibitively high long-term thrombotic risk [26]. A long-term DAPT strategy with Ticagrelor 60 mg b.i.d. in addition to Aspirin has been tested in the
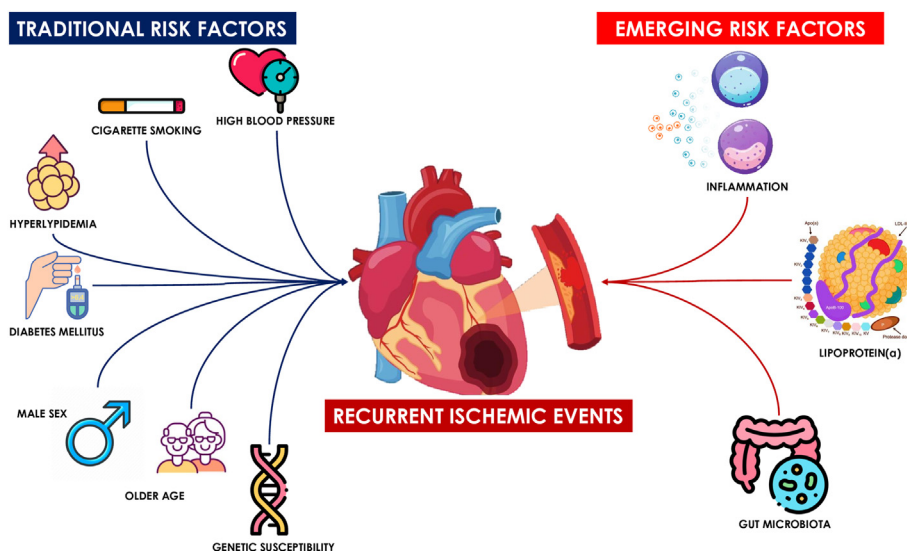

Fig. 1. Traditional and novel risk factors for recurrent ischemic events.

PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis In Myocardial Infarction 54) trial, in which the prolonged DAPT significantly reduced the recurrence of ischemic events in post-MI patients, especially in patients with high atherosclerotic burden, with no difference in terms of fatal and intracranial bleedings [26,27].

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, on the other hand, evaluated an alternative strategy for the prevention of thrombotic events adding to the single antiplatelet therapy with Aspirin a low-dose (2.5 mg b.i.d.) of Rivaroxaban in patients with extensive atherosclerotic disease. This association significantly reduced the incidence of ischemic events, however these patients suffered a higher risk of major bleedings [28].

Given these data, it is essential to adopt a tailored approach for each patient, considering both their thrombotic and hemorrhagic risk, to select the most suitable therapy [29—31].

In this setting LDL-C is a well-proven causative contributor to CAD [32]. Although the introduction of drugs such as statins and ezetimibe have markedly reduced the incidence of ischemic events in patients with CAD [33,34], significant residual risk persists in this patient population even with maximal hypolipidemic therapies [35]. This problem was mitigated with the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which succeeded in further reducing cardiovascular events in patients who failed to reach LDL-C targets despite conventional therapies [36—38]. To seek additional factors associated with residual risk in these patients, several subanalyses of randomized trials have focused on finding further predictors of events [39,40]. In particular, a subanalysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial showed that despite optimally controlled LDL-C levels with PCSK9 inhibitors, high-sensitivity C-reactive protein (hsCRP) was a significant predictor of long-term events [39]. In addition, a prespecified analysis of the ODYSSEY Outcomes study showed that Lipoprotein(a) [Lp(a)] was a strong predictor of long-term ischemic events, independently of LDL-C values [41].

This evidence suggests that there is still a way to go in optimizing the residual cardiovascular risk of patients with CAD and that the aim of future research is to focus on and treat emerging risk factors.

3. Inflammation and atherosclerosis

Inflammation plays a central role in the development and progression of atherosclerosis [42].

Traditional risk factors such as hypertension, cigarette smoking, hyperlipidemia and diabetes can activate endothelial damage and dysfunction promoting a vascular low-grade inflammatory response, leading to the progression of atherosclerosis [43]. On this basis, inflammation represents a common mechanism bridging traditional and emerging CV risk factors to the development of atherosclerosis [44]. Specifically, it has been observed that LDL can activate T cells [45]. Furthermore, hypertension also appears to be linked to inflammatory patterns, as angiotensin II promotes the induction of nuclear transcriptors related to inflammatory response [46]. Moreover, several studies have previously reported that excess visceral adipose tissue associated with insulin resistance can act as a trigger for the release of proinflammatory cytokines [47]. Finally, cigarette smoking is known to correlate with increased inflammatory stimulus. In fact, besides correlating with an increase in leukocytes, an increase in inflammatory markers correlated with smoking has also been observed [48].

Recently, improved outcomes of patients with CAD receiving anti-inflammatory therapies have ignited the debate on the importance of this pathophysiological process in the residual risk of these patients [49—52]. Atherosclerosis is at the core of a chronic vicious circle in which inflammatory cells penetrate the damaged endothelium and there release several proinflammatory cytokines [53—56]. In this environment, the persistence of necrotic endothelial cells, which compose the necrotic core of the atherosclerotic plaque, causes a further activation and promotion of the inflammatory process, leading to a chronic damaging self-fed process [57,58].

Furthermore, a subanalysis of CANTOS (The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial showed a significant lower incidence of ischemic events in post-MI patients with lower hsCRP levels treated with Canakinumab [59]. Moreover, a continuous association between CRP levels and recurrence of CAD has been described in a large metanalysis involving 160,309 subjects from 54 long-term prospective [60].

Recently, inflammasome has been extensively investigated as one of the pivotal regulatory factors in the inflammatory process [61,62], and, considering this evidence, the inflammasome nucleotide-binding oligomerization domain, leucine-rich repeat-containing receptor (NLR) family pyrin

domain-containing 3 (NLRP3) has been broadly analyzed and characterized as being considered one of the key players in atherosclerosis [62].

Cholesterol crystals from atherosclerotic plaque, Ox-PLs, and endothelial wall shear stress appear to be the main triggers of NLRP3 activation [63−65]. When activated, NLRP3 promotes the activation of inerleukin-1β (IL-1β), which possesses numerous proinflammatory effects, stimulating the secretion of additional cytokines and interleukins, through which in addition to sustaining the inflammatory process, also promotes the release of acute-phase factors such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1), promoting the formation of a prothrombotic environment [66−69].

In several studies, elevated IL-1 has been associated with worse ischemia-reperfusion injury as well as increased negative cardiac remodelling while, its inhibition, has been related to decreased negative remodelling and lower release of acute phase factors [70−72].

Based on this evidence, the inflammatory cascade emerges as a crucial factor in the progression of atherosclerosis in patients with CAD, as well as a potential predictor contributing to the residual risk of such patients.

3.1. Anti-inflammatory therapies for CAD patients

Targeting NLRP3 inflammasome and other mediators of inflammation represent an interesting area of research and seems to be a future paradigm in treatment of post-MI patients.

Colchicine is one of the most promising anti-inflammatory drugs used in this type of patient. European Society of Cardiology (ESC) 2021 guidelines on cardiovascular disease prevention suggest that low-dose colchicine (0.5 mg daily) may be considered in secondary prevention, especially if other risk factors are insufficiently controlled or if recurrent cardiovascular events occur under optimal therapy (IIb) [73]. This indication has been based on the results of two randomized trials, COLCOT and LoDoCo2, in which low-dose colchicine was shown to be effectively reducing cardiovascular events in patients with CAD [51,52]. Furthermore, a recent meta-analysis that pooled 11 randomized studies on the use of colchicine in patients with CAD reported a significant reduction in both long-term cardiovascular and cerebrovascular events [74].

Methotrexate (MTX), a widely used antirheumatic drug, has also been tested in patients with CAD. Specifically, a meta-analysis performed including 10 observational studies had previously described a significant reduction in cardiovascular events in patients with rheumatoid arthritis treated with MTX [75]. This finding, though, has not been confirmed in the Cardiovascular Inflammation Reduction trial (CIRT), in which no significant reduction in cardiovascular events was reported in patients with atherosclerotic disease receiving low-dose MTX [76]. The negative result of this study could be related to the drug formulation, therefore a new study investigating the effect of MTX formulated in LDL nanoparticles is currently ongoing and results are expected in the next few years (NCT04616872).

Among immunomodulatory monoclonal antibodies, Canakinumab, administered at a dose of 150 mg every 3 months subcutaneously, has been found to significantly reduce cardiovascular events compared with placebo in the CANTOS study [50]. In addition, in a subanalysis of the same study, a reducing effect on proinflammatory factors, specifically IL-6 and hsCRP, was also documented [59]. Those effects appear to be directly related to its action as a hindrance between IL-1β and its receptor. However, it should be considered that the immunomodulatory effect of this molecule is associated with significant infectious-immunologic adverse effects since the action of this molecule occurs systemically [50].

Two recent randomized trials (ASSAIL-MI and RESCUE) tested the effect of further monoclonal antibodies, Tocilizumab and Ziltivekimab, which antagonize IL-6 and IL-6 ligand, respectively [77,78]. Specifically, Tocilizumab at a dose of 280 mg demonstrated an increase in myocardium salvage after revascularization in patients with STEMI [77], while Ziltivekimab was effective in reducing plasma values of inflammatory and thrombotic biomarkers in the context of advanced renal disease [78].

Finally, two new molecules that can directly target NLRP3 inflammasome, namely arglabin and MCC950, have been shown in several experimental animal models to effectively reduce inflammatory triggers, improve lipid profile, reduce atherosclerotic plaque size, and reduce the area of myocardial infarction [49,79,80]. However, clinical studies in humans are awaited to evaluate the actual benefit of these molecules.

Although anti-inflammatory therapy may represent a future ace in the hole in secondary prevention for patients with CAD, the potential adverse reactions and the cost of such drugs make this option currently extremely limited. Future research should focus on developing effective and safe molecules with affordable costs for patients and national health services.

Table 1 summarizes the emerging antinflammatory therapies.

4. Lipoprotein(a): the "new" actor in atheroscleorosis

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein composed of an LDL-rich particle and an apolipoprotein B100 molecule bound via a single disulphide link to apolipoprotein(a) [apo(a)], a plasminogen-like glycoprotein [81]. [43] Its plasma levels are mostly genetically determined and varies from <0.1 mg/dL to >300 mg/dL (<0.2–750 nmol/L), generally (>90% of the cases) with no significant influence from dietary and environmental factors [81].

Lp(a) has been described as a supplemental actor in the pathogenesis of atherosclerosis, participating in foam cell formation, smooth muscle cell proliferation, inflammation, and plaque instability [82]. These effects are not only related through similar LDL mechanisms, but also to specific aop(a)-related pathways. Apo(a) exhibits a high affinity for damaged vascular endothelium due to lysine binding sites that interact directly with the exposed portions of endothelium, allowing its subintimal entry and deposition [83]. In addition, apo(a) can actively interfere in the fibrinolysis process and promote a prothrombotic status due to its plasminogen-like structure [84].

In addition, Lp(a) promotes atherogenosis and inflammation by behaving as a carrier for Ox-PLs within the endothelium [85]. In fact, in a study involving patients with elevated Lp(a) levels, excessive accumulation of 18-fluorodeoxyglucose within the vascular walls, itself an indication of inflammation, was documented, with additional increased reactivity of inflammatory cells [86].

4.1. Lipoprotein(a) in cardiovascular prevention

Over the past years, several primary prevention studies conducted in healthy patients with no history of atherosclerosis have shown that plasma Lp(a) levels exhibit a linear and independent association in the development of atherosclerotic cardiovascular disease (ASCVD) [87–91]. The Copenhagen City Heart Study showed an increased risk of cardiovascular events in healthy subjects, linearly associated with plasma Lp(a) levels at a 10-year follow-up, especially for subjects with extremely high Lp(a) plasma levels [87]. In an individual patient data meta-analysis including 7 randomized clinical studies, a linear association has been observed between the risk of cardiovascular events and plasma Lp(a) levels, independently of C-LDL values and with hypolipidemic drugs treatments [92]. Moreover, both Lp(a) and small isoforms of apo(a) have emerged as independent causal factors of CAD in a recent Mendelian randomization study involving nearly 17 thousand patients [93].

This evidence affirmed Lp(a) as an independent risk factor for atherosclerotic cardiovascular disease, driving exponential interest in the development of therapies that could impact its plasma levels and

Table 1. Anti-inflammatory and immune therapies in patients with established CAD.

Drug	Principal mechanism of action	Study	Findings
Colchicine	Inhibition of microtubules polymerisation	COLCOT (NCT02551094) LoDoCo2 (ACTRN12614000093684)	Colchicine 0.5 mg significantly reduced the risk of ischemic CV events
Canakinumab	Anti-IL-1β monoclonal antibody	CANTOS (NCT01327846)	Canakinumab 150 mg every 3 months significantly reduced the rate of recurrent CV events
Methotrexate	Folate pathway antagonist	CIRT (NCT01594333)	MTX 15–20 mg weekly did not reduce levels of IL-1β, IL-6, or CRP and did not reduce CV events; a phase III RCT evaluating MTX delivered in LDL-nanoparticle is ongoing (NCT04616872)
Anakinra	Inhibition of the interaction between IL-1 and IL-1R	VCU-ART3 (NCT01950299)	Anakinra significantly reduces the systemic inflammatory response after STEMI
Tocilizumab	Inhibits IL-6R	ASSAIL-MI (NCT03004703)	Tocilizumab increased myocardial salvage; no difference in terms of CV outcomes
Ziltivekimab	Inhibits IL-6 ligand	RESCUE (NCT03926117)	Ziltivekimab reduced biomarkers of inflammation and thrombosis; phase III RCT evaluating the effect on CV outcomes is ongoing (NCT05021835)

CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular events; hs-CRP, high-sensitivity C-reactive protein; IL-1, interleukin-1; IL-1R, interleukin-1 receptor; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; LDL, low density lipoprotein; MI, myocardial infarction; MTX, methotrexate; MVD, multivessel disease; STEMI, ST-elevation myocardial infarction; Pts, patients; RCT, randomized controlled trial.

activity. Noteworthy, measuring Lp(a) at least once in adults, preferably in the first lipid profile has been recommended by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), with a desirable plasma level <30 mg/dL [94].

Several studies have recently evaluated the role of Lp(a) in the secondary prevention of patients with established CAD [7,40,95−102].

The Copenhagen General Population Study described that patients with established ASCVD and with high Lp(a) levels (≥50 mg/dL) suffer a higher risk of major cardiovascular events (MACE), regardless of C-LDL levels [103]. Moreover, a sub-analysis of the ODISSEY Outcomes trial, which evaluated the effect of alirocumab vs. placebo in post-MI patients, found an independent linear association between Lp(a) plasma levels and risk of MACE and, furthermore, the reduction on Lp(a) plasma levels provided by alirocumab was significantly associated with a reduction in long-term MACEs [40]. Furthermore, a real-world observational study conducted on 12064 post-PCI described a significant and independent association between high Lp(a) levels and the long-term risk of repeated revascularization [102]. Finally, Lp(a) levels seems to better predict the risk of recurrence of ischemic events in patients without history of diabetes [99].

These data yield robust evidence for the consideration of Lp(a) as an integrative prognostic factor in patients with estabilished CAD and highlight the emergent need toward the development of therapies that will be effective in reducing its plasma levels.

4.2. Current and emerging therapies for high lipoprotein(a)

To date, there are no approved pharmacological agents targeting specifically Lp(a) nor preliminary data from randomized clinical trial on Lp(a) reduction and, the only effective treatment is lipoprotein apheresis, which is an invasive procedure, suitable only for secondary prevention in patients with extremely high Lp(a) levels and recurrent cardiovascular events despite optimal medical therapy [104].

Statins, a cornerstone of dyslipidemia treatment, still they have not shown any benefit in reducing Lp(a) plasma levels [105]. Conversely, niacin has shown in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) study a discrete reduction in Lp(a) values of about 20% without, however, significantly decreasing the cardiovascular risk of the enrolled patients [97].

Different phase 3 trials have found a positive effect of mipomersen (an antisense oligonucleotide targeting apolipoprotein B synthesis) in reducing Lp(a) levels by 26%, however its effect on the prognosis in patients with CAD has not yet been tested [106].

Data from the randomized trials FOURIER and ODISSEY Outcomes, which tested the effect of PCSK9 inhibitors in patients with established CAD, respectively of evolocumab and alirocumab, showed not only a significant reduction in Lp(a) levels in these patients, but also a clinical benefit in terms of reduction of long-term cardiovascular events, independently from other serum lipoproteins [41,101].

Furthermore, in the ORION-10 and ORION-11 trials, Inclisiran, a small-interfering (siRNA) PCSK) inhibitor, showed a positive effect in decreasing Lp(a) plasma levels; however its clinical impact has not yet been tested in secondary prevention patients [107].

Moreover, ESC/EAS guidelines recommends the use of PCSK9 inhibitors in patients with familial hypercholesterolemia and high Lp(a) (IIa) [108].

Finally, novel apo(a)-specific target therapies are being investigated through Pelacarsen and Olpasiran drugs (phases II and III), which have exhibited favorable results in terms of reducing Lp(a) plasma values, while prognostic outcome data are expected in the forthcoming years [109−111].

Table 2 summarizes the emerging lowering Lp(a) therapies.

5. Gut microbiota

Gut microbiota is composed of several microbes colonising the whole digestive tract and its composition and functioning could be affected by genetic, dietary, and environmental factors [112,113]. Innate immunity is constantly engaged in compensating the chronic inflammatory trigger generated by microbiota agents themselves [114]. The microbiota's composition could be deeply impaired by a condition known as gut dysbiosis, which could take part in the pathogenesis of several intestinal and non-intestinal diseases such as diabetes, obesity, and cerebrovascular diseases [115]. Recently, it has been investigated that alterations in the microbiota may promote the crossing within the systemic circulation of particular bacterial products such as lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO) which may trigger atherothrombotic and ischemic cardiovascular events [73,116]. However, controversial results have been brought from

Table 2. Emerging therapies for lowering Lp(a) serum level.

Drug	Principal mechanism of action	Mechanism of Lp(a) lowering	Study	Findings
Evolocumab	Monoclonal antibody inhibiting LDL-R degradation by targeting PCSK9	Inhibition of apo(a) secretion	FOURIER (NCT01764633)	Evolocumab significantly reduced Lp(a) by a median of 26.9%; Evolocumab reduced the risk of death, MI, or PCI by 23% in patients with a baseline Lp(a) > median value.
Alirocumab	Monoclonal antibody inhibiting LDL-R degradation by targeting PCSK9	Inhibition of apo(a) secretion	ODISSEY Outcomes (NCT01663402)	Alirocumab significantly reduced Lp(a) by 23%; Alirocumab independently reduced the risk of CV adverse outcomes.
Inclisiran	siRNA inhibiting LDL-R degradation targeting PCSK9	Inhibition of apo(a) secretion	ORION-10 ORION-11 (NCT03399370; NCT03400800)	Inclisiran reduces Lp(a) plasma levels by 19–22%; The effects on CV outcomes is unknown.
Mipomersen	ASO inhibiting apo(B) synthesis	–	Four phase III trials (NCT00607373; NCT00706849; NCT00770146; NCT00794664)	Mipomersen reduced Lp(a) plasma levels from 20% to 40%; The effects on CV outcomes is unknown.
Olpasiran	siRNA targeting apo(a) mRNA and leads to degradation	–	OCEAN[a]-DOSE (NCT04270760)	Olpasiran reduced Lp(a) plasma levels from 67% to 97%; The effect on CV outcomes is unclear.
Pelacarsen	ASO targeting apo(a) mRNA and leads to degradation	–	AKCEA-APO(a)-LRx (NCT03070782)	Pelacarsen reduced Lp(a) plasma levels by 80%. A phase III RCT evaluating the effect on CV outcomes is ongoing (NCT04023552)

ACS, acute coronary syndromes; Apo(a), apolipoprotein(a); Apo(B), apolipoprotein(B); ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-R, low density lipoprotein receptor; Lp(a), lipoprotein(a); MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, Proprotein convertase subtilisin/kexin type 9; Pts, patients; RCT, randomized controlled trial; siRNA, small-interfering RNA.

small clinical studies investigating the association between TMAO and atherosclerotic cardiovascular events and its effect in atherosclerosis has been observed only in animal models [117–122].

Considerable interest, however, is growing on the possibility that LPS may play a role in the development of ASCVD through a low-grade endotoxemia induced by itself [123]. Due to its interaction with toll-like receptors, which are located on several cellular walls, it has been associated with the development of thrombotic phenomena [124]. Moreover, studies conducted in healthy subjects, highlighted the association between the soluble levels of LPS and the risk of ASCVD [125–127]. An enhanced gut permeability has been observed in patients suffering a MI and circulating levels of LPS were associated with thrombus burden in patients with STEMI in a small case-control study [128]. Recently, an observational study of post-STEMI patients found that LPS circulating levels occurring during MI were significantly associated with the long-term risk of adverse cardiovascular events [129]. However,

current evidence on the role of dysbiosis and bacterial proteins in predicting future adverse events in patients with CAD is strongly limited, and their role in prognostic stratification of these patients remains unclear.

Fiber-rich diets such as the Mediterranean diet, the use of prebiotics and probiotics, and fecal microbiome transplants have been demonstrated to be beneficial in positively regulating intestinal permeability and in lowering the circulating levels of bacterial products. However, these effects have not yet been analyzed in randomized clinical trials or studies with strong statistical power [116,123].

6. Conclusions and future perspectives

Despite the optimization of secondary prevention strategies, and the approval of new drugs, post-ACS patients still have a non-negligible risk of long-term adverse events. The residual risk of these patients is affected by several interacting factors forming a complex pathophysiological patchwork.

A wide-ranging and tailored approach is required to minimize the occurrence of long-term adverse events.

The chronic inflammatory stimulus represents one of the key players in the atherosclerotic process, and recent studies on the effect of anti-inflammatory drugs on cardiovascular risk have yielded promising results. However, the safety profile of these drugs and their cost-effectiveness is still to be clarified.

Lp(a) is one of the most promising emerging risk factors, and several studies have established its long-term prognostic value. Several studies are ongoing to develop specific drugs to influence its plasma values and pathogenic activity.

The study of gut microbiome and the effects of dysbiosis is a field that is gaining considerable interest in different clinical settings. Its correlation with atherothrombotic events and the possibility of targeting it could represent a breakthrough for the future therapies of these patients.

Finally, the future cardiology should increasingly focus on seeking out peculiar factors that may contribute to the residual risk of patients with CAD with the goal of specifically targeting them.

Funding

Conflicts of interest

No conflict of interest to declare.

References

[1] De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Relationship between patient's risk profile and benefits in mortality from adjunctive abciximab to mechanical revascularization for ST-segment elevation myocardial infarction: a meta-regression analysis of randomized trials. J Am Coll Cardiol 2006;47(3):685—6.
[2] Verdoia M, Schaffer A, Barbieri L, Cassetti E, Piccolo R, Galasso G, et al. Benefits from new ADP antagonists as compared with clopidogrel in patients with stable angina or acute coronary syndrome undergoing invasive management: a meta-analysis of randomized trials. J Cardiovasc Pharmacol 2014;63(4):339—50.
[3] Costa F, Montalto C, Branca M, Hong SJ, Watanabe H, Franzone A, et al. Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: a meta-analysis of randomized trials. Eur Heart J 2023 Mar 14;44(11):954—68. https://doi.org/10.1093/eurheartj/ehac706. PMID: 36477292.
[4] De Luca G, Smits P, Hofma SH, Di Lorenzo E, Vlachojannis GJ, Van't Hof AWJ, et al. Everolimus eluting stent vs first generation drug-eluting stent in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Int J Cardiol 2017;244:121—7.
[5] De Luca G, Schaffer A, Wirianta J, Suryapranata H. Comprehensive meta-analysis of radial vs femoral approach in primary angioplasty for STEMI. Int J Cardiol 2013;168(3):2070—81.
[6] Bellino M, Silverio A, Esposito L, Cancro FP, Ferruzzi GJ, Di Maio M, et al. Moving toward precision medicine in acute coronary syndromes: a multimodal assessment of non-culprit lesions. J Clin Med 2023;12(13).
[7] Galasso G, De Angelis E, Silverio A, Di Maio M, Cancro FP, Esposito L, et al. Predictors of recurrent ischemic events in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2021;159:44—51.
[8] De Luca G, Dirksen MT, Spaulding C, Kelbæk H, Schalij M, Thuesen L, et al. Time course, predictors and clinical implications of stent thrombosis following primary angioplasty. Insights from the DESERT cooperation. Thromb Haemostasis 2013;110(4):826—33.
[9] Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36(19):1163—70.
[10] De Rosa R, Silverio A, Varricchio A, De Luca G, Di Maio M, Radano I, et al. Meta-analysis comparing outcomes after everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents in patients with acute coronary syndromes. Am J Cardiol 2018;122(1):61—8.
[11] Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. Eur Heart J 2016;37(22):1720—2.
[12] De Luca G, Verdoia M, Cassetti E, Schaffer A, Cavallino C, Bolzani V, et al. High fibrinogen level is an independent predictor of presence and extent of coronary artery disease among Italian population. J Thromb Thrombolysis 2011;31(4):458—63.
[13] Barbieri L, Verdoia M, Schaffer A, Marino P, Suryapranata H, De Luca G. Impact of sex on uric acid levels and its relationship with the extent of coronary artery disease: a single-centre study. Atherosclerosis 2015;241(1):241—8.
[14] Verdoia M, Barbieri L, Di Giovine G, Marino P, Suryapranata H, De Luca G. Neutrophil to lymphocyte ratio and the extent of coronary artery disease: results from a large cohort study. Angiology 2016;67(1):75—82.
[15] Silverio A, Cancro FP, Esposito L, Bellino M, D'Elia D, Verdoia M, et al. Secondary cardiovascular prevention after acute coronary syndrome: emerging risk factors and novel therapeutic targets. J Clin Med 2023;12(6).
[16] Esposito L, Di Maio M, Silverio A, Cancro FP, Bellino M, Attisano T, et al. Treatment and outcome of patients with coronary artery ectasia: current evidence and novel opportunities for an old dilemma. Front Cardiovasc Med 2021;8:805727.
[17] Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, et al. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation 2001;103(7):934—40.
[18] Rioufol G, Finet G, Ginon I, André-Fouët X, Rossi R, Vialle E, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. Circulation 2002;106(7):804—8.
[19] Roleder-Dylewska M, Gasior P, Hommels TM, Roleder T, Berta B, Ang HY, et al. Morphological characteristics of lesions with thin cap fibroatheroma-a substudy from the COMBINE (OCT-FFR) trial. Eur Heart J Cardiovasc Imaging 2023;24(5):687—93. https://doi.org/10.1093/ehjci/jeac218.
[20] Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, AJJ IJ, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. Eur Heart J 2021;42(45):4671—9.
[21] Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304(12):1350—7.

[22] Kereiakes DJ, Yeh RW, Massaro JM, Cutlip DE, Steg PG, Wiviott SD, et al. DAPT score utility for risk prediction in patients with or without previous myocardial infarction. J Am Coll Cardiol 2016;67(21):2492—502.

[23] Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes 2012;5(4):532—40.

[24] Kern DM, Mellström C, Hunt PR, Tunceli O, Wu B, Westergaard M, et al. Long-term cardiovascular risk and costs for myocardial infarction survivors in a US commercially insured population. Curr Med Res Opin 2016;32(4):703—11.

[25] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364(3):226—35.

[26] Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372(19):1791—800.

[27] Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol 2016;67(23):2719—28.

[28] Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in stable cardiovascular disease. N Engl J Med 2017;377(14):1319—30.

[29] Silverio A, Di Maio M, Buccheri S, De Luca G, Esposito L, Sarno G, et al. Validation of the academic research consortium high bleeding risk criteria in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis of 10 studies and 67,862 patients. Int J Cardiol 2022;347:8—15.

[30] Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140(3):240—61.

[31] Scudiero F, Canonico ME, Sanna GD, Dossi F, Silverio A, Galasso G, et al. Dual Antiplatelet therapy with 3rd generation P2Y12 inhibitors in STEMI patients: impact of body mass index on loading dose-response. Cardiovasc Drugs Ther 2023 Aug;37(4):695—703. https://doi.org/10.1007/s10557-022-07322-2. Epub 2022 Feb 17. PMID: 35175499.

[32] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38(32):2459—72.

[33] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (London, England) 2010;376(9753):1670—81.

[34] Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016;316(12):1289—97.

[35] Silverio A, Benvenga RM, Piscione F, Gulizia MM, Meessen J, Colivicchi F, et al. Prevalence and predictors of out-of-target LDL cholesterol 1 to 3 Years after myocardial infarction. A subanalysis from the eyeshot post-MI registry. J Cardiovasc Pharmacol Therapeut 2021;26(2):149—57.

[36] Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376(18):1713—22.

[37] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379(22):2097—107.

[38] Bellino M, Galasso G, Silverio A, Tedeschi M, Formisano C, Romei S, et al. Soluble PCSK9 inhibition: indications, clinical impact, new molecular insights and practical approach-where do we stand? J Clin Med 2023;12(8).

[39] Bohula EA, Giugliano RP, Leiter LA, Verma S, Park JG, Sever PS, et al. Inflammatory and cholesterol risk in the FOURIER trial. Circulation 2018;138(2):131—40.

[40] Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol 2020;75(2):133—44.

[41] Szarek M, Bittner VA, Aylward P, Baccara-Dinet M, Bhatt DL, Diaz R, et al. Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial. Eur Heart J 2020;41(44):4245—55.

[42] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352(16):1685—95.

[43] Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. J Am Coll Cardiol 2018;72(17):2071—81.

[44] Libby P. The changing landscape of atherosclerosis. Nature 2021;592(7855):524—33.

[45] Ketelhuth DF, Hansson GK. Adaptive response of T and B cells in atherosclerosis. Circ Res 2016;118(4):668—78.

[46] Kranzhöfer R, Browatzki M, Schmidt J, Kübler W. Angiotensin II activates the proinflammatory transcription factor nuclear factor-kappaB in human monocytes. Biochem Biophys Res Commun 1999;257(3):826—8.

[47] Rocha VZ, Folco EJ, Sukhova G, Shimizu K, Gotsman I, Vernon AH, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. Circ Res 2008;103(5):467—76.

[48] Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004;43(10):1731—7.

[49] van Hout GP, Bosch L, Ellenbroek GH, de Haan JJ, van Solinge WW, Cooper MA, et al. The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction. Eur Heart J 2017;38(11):828—36.

[50] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377(12):1119—31.

[51] Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383(19):1838—47.

[52] Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381(26):2497—505.

[53] Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull Jr W, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92(5):1355—74.

[54] Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. Circulation 1995;92(5):1084—8.

[55] Frostegård J, Ulfgren AK, Nyberg P, Hedin U, Swedenborg J, Andersson U, et al. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. Atherosclerosis 1999;145(1):33—43.

[56] van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89(1):36—44.

[57] Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell 2011;145(3):341–55.

[58] Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. Circ Res 2014;114(12):1867–79.

[59] Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet (London, England) 2018;391(10118):319–28.

[60] Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet (London, England) 2010;375(9709):132–40.

[61] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464(7293):1357–61.

[62] Schroder K, Tschopp J. The inflammasomes. Cell 2010; 140(6):821–32.

[63] Xiao H, Lu M, Lin TY, Chen Z, Chen G, Wang WC, et al. Sterol regulatory element binding protein 2 activation of NLRP3 inflammasome in endothelium mediates hemodynamic-induced atherosclerosis susceptibility. Circulation 2013;128(6):632–42.

[64] Rajamäki K, Lappalainen J, Oörni K, Välimäki E, Matikainen S, Kovanen PT, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. PLoS One 2010;5(7):e11765.

[65] Yeh M, Cole AL, Choi J, Liu Y, Tulchinsky D, Qiao JH, et al. Role for sterol regulatory element-binding protein in activation of endothelial cells by phospholipid oxidation products. Circ Res 2004;95(8):780–8.

[66] He Y, Hara H, Núñez G. Mechanism and regulation of NLRP3 inflammasome activation. Trends Biochem Sci 2016; 41(12):1012–21.

[67] Libby P. Interleukin-1 beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol 2017;70(18):2278–89.

[68] Wang JM, Sica A, Peri G, Walter S, Padura IM, Libby P, et al. Expression of monocyte chemotactic protein and interleukin-8 by cytokine-activated human vascular smooth muscle cells. Arterioscler Thromb 1991;11(5): 1166–74.

[69] Loppnow H, Libby P. Adult human vascular endothelial cells express the IL6 gene differentially in response to LPS or IL1. Cell Immunol 1989;122(2):493–503.

[70] Suzuki K, Murtuza B, Smolenski RT, Sammut IA, Suzuki N, Kaneda Y, et al. Overexpression of interleukin-1 receptor antagonist provides cardioprotection against ischemia-reperfusion injury associated with reduction in apoptosis. Circulation 2001;104(12 Suppl 1). I308-i3.

[71] Abbate A, Dinarello CA. Anti-inflammatory therapies in acute coronary syndromes: is IL-1 blockade a solution? Eur Heart J 2015;36(6):337–9.

[72] Morton AC, Rothman AM, Greenwood JP, Gunn J, Chase A, Clarke B, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. Eur Heart J 2015;36(6):377–84.

[73] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227–337.

[74] Andreis A, Imazio M, Piroli F, Avondo S, Casula M, Paneva E, et al. Efficacy and safety of colchicine for the prevention of major cardiovascular and cerebrovascular events in patients with coronary artery disease: a systematic review and meta-analysis on 12 869 patients. Eur J Prev Cardiol 2022;28(17):1916–25.

[75] Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernán MA, Ridker PM, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 2011;108(9):1362–70.

[76] Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019; 380(8):752–62.

[77] Broch K, Anstensrud AK, Woxholt S, Sharma K, Tøllefsen IM, Bendz B, et al. Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. J Am Coll Cardiol 2021;77(15):1845–55.

[78] Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ivkovic M, et al. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet (London, England) 2021;397(10289):2060–9.

[79] Abderrazak A, Couchie D, Mahmood DF, Elhage R, Vindis C, Laffargue M, et al. Anti-inflammatory and anti-atherogenic effects of the NLRP3 inflammasome inhibitor arglabin in ApoE2.Ki mice fed a high-fat diet. Circulation 2015;131(12):1061–70.

[80] Jiang M, Li R, Lyu J, Li X, Wang W, Wang Z, et al. MCC950, a selective NLPR3 inflammasome inhibitor, improves neurologic function and survival after cardiac arrest and resuscitation. J Neuroinflammation 2020;17(1):256.

[81] Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). J Lipid Res 2016;57(8):1339–59.

[82] Boffa MB, Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for atherosclerosis and thrombosis: mechanistic insights from animal models. Clin Biochem 2004;37(5): 333–43.

[83] Nielsen LB. Atherogenecity of lipoprotein(a) and oxidized low density lipoprotein: insight from in vivo studies of arterial wall influx, degradation and efflux. Atherosclerosis 1999;143(2):229–43.

[84] Deb A, Caplice NM. Lipoprotein(a): new insights into mechanisms of atherogenesis and thrombosis. Clin Cardiol 2004;27(5):258–64.

[85] Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med 2005;353(1):46–57.

[86] van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. Circulation 2016;134(8):611–24.

[87] Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation 2008;117(2):176–84.

[88] Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301(22): 2331–9.

[89] Tsimikas S, Mallat Z, Talmud PJ, Kastelein JJ, Wareham NJ, Sandhu MS, et al. Oxidation-specific biomarkers, lipoprotein(a), and risk of fatal and nonfatal coronary events. J Am Coll Cardiol 2010;56(12):946–55.

[90] Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302(4):412–23.

[91] Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009; 361(26):2518–28.

[92] Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events:

individual patient-data meta-analysis of statin outcome trials. Lancet (London, England) 2018;392(10155):1311—20.

[93] Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, et al. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis. Lancet Diabetes Endocrinol 2017;5(7):524—33.

[94] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43(39):3925—46.

[95] Schwartz GG, Ballantyne CM, Barter PJ, Kallend D, Leiter LA, Leitersdorf E, et al. Association of lipoprotein(a) with risk of recurrent ischemic events following acute coronary syndrome: analysis of the dal-outcomes randomized clinical trial. JAMA Cardiol 2018;3(2):164—8.

[96] Gencer B, Rigamonti F, Nanchen D, Vuilleumier N, Kern I, Aghlmandi S, et al. Prognostic value of elevated lipoprotein(a) in patients with acute coronary syndromes. Eur J Clin Invest 2019;49(7):e13117.

[97] Albers JJ, Slee A, O'Brien KD, Robinson JG, Kashyap ML, Kwiterovich Jr PO, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (atherothrombosis intervention in metabolic syndrome with low HDL/high Triglyceride and impact on global health outcomes). J Am Coll Cardiol 2013; 62(17):1575—9.

[98] Zewinger S, Kleber ME, Tragante V, McCubrey RO, Schmidt AF, Direk K, et al. Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study. Lancet Diabetes Endocrinol 2017;5(7):534—43.

[99] Silverio A, Cancro FP, Di Maio M, Bellino M, Esposito L, Centore M, et al. Lipoprotein(a) levels and risk of adverse events after myocardial infarction in patients with and without diabetes. J Thromb Thrombolysis 2022;54(3):382—92.

[100] O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. J Am Coll Cardiol 2014;63(6):520—7.

[101] O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019;139(12): 1483—92.

[102] Yoon YH, Ahn JM, Kang DY, Lee PH, Kang SJ, Park DW, et al. Association of lipoprotein(a) with recurrent ischemic events following percutaneous coronary intervention. JACC Cardiovasc Interv 2021;14(18):2059—68.

[103] Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-Lowering by 50 mg/dL (105 nmol/L) may Be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. Arterioscler Thromb Vasc Biol 2020;40(1):255—66.

[104] Thompson GR. Recommendations for the use of LDL apheresis. Atherosclerosis 2008;198(2):247—55.

[105] Tsimikas S, Gordts P, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. Eur Heart J 2020; 41(24):2275—84.

[106] Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. Arterioscler Thromb Vasc Biol 2015; 35(3):689—99.

[107] Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382(16):1507—19.

[108] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111—88.

[109] O'Donoghue ML, Rosenson RS, Gencer B, López JAG, Lepor NE, Baum SJ, et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. N Engl J Med 2022; 387(20):1855—64.

[110] Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, Tardif JC, Baum SJ, Steinhagen-Thiessen E, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med 2020;382(3):244—55.

[111] Koren MJ, Moriarty PM, Baum SJ, Neutel J, Hernandez-Illas M, Weintraub HS, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med 2022;28(1):96—103.

[112] Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science (New York, NY) 2005;307(5717):1915—20.

[113] Tousoulis D, Guzik T, Padro T, Duncker DJ, De Luca G, Eringa E, et al. Mechanisms, therapeutic implications, and methodological challenges of gut microbiota and cardiovascular diseases: a position paper by the ESC Working Group on Coronary Pathophysiology and Microcirculation. Cardiovasc Res 2022;118(16):3171—82.

[114] Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 2008; 57(6):1470—81.

[115] Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 2016; 22(10):1079—89.

[116] Ascher S, Reinhardt C. The gut microbiota: an emerging risk factor for cardiovascular and cerebrovascular disease. Eur J Immunol 2018;48(4):564—75.

[117] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19(5):576—85.

[118] Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472(7341): 57—63.

[119] Senthong V, Li XS, Hudec T, Coughlin J, Wu Y, Levison B, et al. Plasma trimethylamine N-oxide, a gut microbe-generated phosphatidylcholine metabolite, is associated with atherosclerotic burden. J Am Coll Cardiol 2016;67(22): 2620—8.

[120] Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WH. Trimethylamine N-oxide and mortality risk in patients with peripheral artery disease. J Am Heart Assoc 2016; 5(10).

[121] Mueller DM, Allenspach M, Othman A, Saely CH, Muendlein A, Vonbank A, et al. Plasma levels of trimethylamine-N-oxide are confounded by impaired kidney function and poor metabolic control. Atherosclerosis 2015; 243(2):638—44.

[122] Skagen K, Trøseid M, Ueland T, Holm S, Abbas A, Gregersen I, et al. The Carnitine-butyrobetaine-trimethylamine-N-oxide pathway and its association with cardiovascular mortality in patients with carotid atherosclerosis. Atherosclerosis 2016;247:64—9.

[123] Violi F, Cammisotto V, Bartimoccia S, Pignatelli P, Carnevale R, Nocella C. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. Nat Rev Cardiol 2023;20(1):24—37.

[124] den Dekker WK, Cheng C, Pasterkamp G, Duckers HJ. Toll like receptor 4 in atherosclerosis and plaque destabilization. Atherosclerosis 2010;209(2):314—20.

[125] Wiedermann CJ, Kiechl S, Dunzendorfer S, Schratzberger P, Egger G, Oberhollenzer F, et al. Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. J Am Coll Cardiol 1999;34(7):1975—81.

[126] Asada M, Oishi E, Sakata S, Hata J, Yoshida D, Honda T, et al. Serum lipopolysaccharide-binding protein levels and

the incidence of cardiovascular disease in a general Japanese population: the hisayama study. J Am Heart Assoc 2019;8(21):e013628.

[127] Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. Arterioscler Thromb Vasc Biol 2007;27(6):1433–9.

[128] Carnevale R, Sciarretta S, Valenti V, di Nonno F, Calvieri C, Nocella C, et al. Low-grade endotoxaemia enhances artery thrombus growth via Toll-like receptor 4: implication for myocardial infarction. Eur Heart J 2020;41(33):3156–65.

[129] Zhou X, Li J, Guo J, Geng B, Ji W, Zhao Q, et al. Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction. Microbiome 2018;6(1):66.