



Are current systemic endothelial anti-inflammatory therapies effective/safe, and only in secondary prophylaxis?

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Abstract

The focus of this paper is inflammation of the endothelium – originating in situ or exogenous – in the context of general inflammatory diseases, including autoimmune, in which it is accelerated. The main triggers or accelerators include hypertension caused by the hyperexpression of angiotensin II, which triggers endothelial inflammation and dyslipidemia by LDL cholesterol in small, dense and oxidized fractions. Others include hyperapoprotein B, or an increase in lipoprotein(a); hypertriglyceridemia associated with hypoHDL, as in atherogenic dyslipidemia in diabetes mellitus; dysglycemia, more specifically hyperglycemic spikes; and hyperinsulinism, which has been implicated in the acceleration of endothelial inflammation, especially in middle-aged patients (39-56 years). New data is based not only on genetic information, but also on morphological studies and new markers of endothelial inflammation. In this case, the reaction of lymphocytokines, including blood components such as lympho-monocytes but also platelets, can contribute to the precipitation of atherothrombotic phenomena with a predominantly inflammatory- prothrombotic mechanism. Existing lipid-lowering therapies did not provide complete protection, even in secondary prophylaxis using maximum tolerated doses of potent statins + ezetimibe. We will be able to see, in the near future, the results of adequate therapies to control the values of lipoprotein(a) and apolipoprotein B, which have proven to be even more statistically strong ischemic risk factors than LDL cholesterol, especially non-HDL cholesterol. With regard to the control of lipid fractions, some do not appear in the prevention guidelines, and perhaps this is unjustified. These include antisense oligonucleotides (ASOs) and small-interfering RNA (siRNA). There are also agents still in the investigation stage: pelacarsen (ASO); olpasiran (siRNA); zerlasiran (siRNA); lepodisiran (siRNA); and muvalaplin (oral therapy). Favorable effects were also obtained with niacin and evolocumab, but not of the same magnitude. We quantify the inflammatory risk using either indirect markers – such as CRPs, or the induction of endothelial alteration in association with lymphocytokines. We also do this directly, by dosing more reliable markers such as interleukin 1 and 6, and earlier interleukin 8 and MCP 1; then TNF α ; interferon β 1; soluble vascular adhesion molecules (VCAM-1); phospholipase A2 associated with circulating lipoproteins (FLPA2); IGF-1 (insulin-like growth factor-1); soluble molecules of selectin-E and -P; glycation end products (PFG); blood level of NO; and increased serum content of peroxynitrite (ONOO-), which is the product of interaction product between NO and the superoxide anion. Several studies have evaluated the effect of colchicine in patients with coronary ischemic disease. This drug prevents the polymerization of microtubules by interfering with the function of leukocytes. LODOCO II, COLCOT, CLEAR16 studies, only the last inconclusive for the prophylactic effect of colchicine. Studies with interleukin inhibitors/chemokine inhibitors, CANTOS – with canakinumab; Virginia Commonwealth University-Anakinra remodeling trial 38, with anakinra; and RESCUE, with ziltivekimab. There are some sources of hope, including predominantly non-anti-inflammatory drugs, statins, and proprotein inhibitors that convert subtilisin/kexin type 9 (PCSK9); GLP1 agonists, small and interfering RNA-based therapies; and gene addition and editing (CRISPR), including regularly clustered short palindromic repeats and base editing. The major question, despite the current economic problems, is: wouldn't systemic endothelial anti-inflammatory therapies (not necessarily those already tested), in patients at high risk and with evidence of inflammation, be effective in primary prophylaxis? Until now, no such studies have been done in significant batches, at least not randomized trials. Primary prophylaxis is, in the 21st century, another conceptual stage in the development of life-saving therapies, not only to prolong life, but also for the healthy living of the population.

Keywords

Atherosclerosis/atherothrombosis, “vulnerable” plaque, residual inflammatory risk, lipid-lowering treatments, primary endothelial anti-inflammatory treatments, primary non-anti-inflammatory therapies, secondary atherothrombotic prevention studies with anti-inflammatories

Rezumat

Focusul acestei treceri în revistă este “Inflamația endotelială” – originară, in situ, sau exogenă – în contextul bolilor inflamatorii generale – inclusiv autoimune, accelerată de condițiile de dezvoltare a unei inflamații. Principalii factori trigger sau acceleratori sunt hipertensiunea cauzată de hiperexpresia Angiotensinei 2 – declanșator al inflamației endoteliale, dislipidemie – de colesterolul LDL – fracțiuni mici, dense și oxidate, dar și hiperApolipoproteină B sau creșterea a Lipoproteinei(a), hipertrigliceridemia asociată cu hypoHDL, ca în dislipidemia aterogenă din diabetul zaharat, disglicemia, mai precis spik-urile hiperglicemice, precum și hiperinsulinismul fiind incriminate în accelerarea inflamației endoteliale, în special la pacienții de vârstă mijlocie (39-56 ani). Noile date, bazate nu numai

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pe informații genetice, ci și pe studii morfologice și noi markeri ai inflamației endoteliale - în acest caz reacția limfocitokinelor, inclusiv pe reacția componentelor sanguine - limfo-monocite, dar și trombocite - pot contribui la precipitarea fenomenelor aterotrombotice, cu un mecanism predominant inflamator - protrombotic. Terapia actuală de scădere a lipidelor nu a oferit protecție completă, chiar și în profilaxia secundară, folosind doze maxime tolerate de statine puternice + ezetimib; vom putea vedea, în viitorul apropiat, rezultatele terapiei adecvate pentru a controla valorile lipoproteinei(a) și apolipoproteinei B, care s-au dovedit a fi factori de risc ischemici și mai puternici statistic decât colesterolul LDL și, în special, colesterolul non-HDL. Vorbind despre controlul fracțiunilor lipidice sunt molecule care nu apar în ghidurile de prevenție în mod nejustificat astăzi: oligonucleotide antisens (ASO), ARN cu interferență mică (siARN), precum și agenți încă în stadiul de investigație: 1. Pelacarsen (ASO); 2. Olpasiran (siARN) 3. Zelasiran (siARN). 4. Lepodisiran (siARN) 5. Muvalaplin (terapie orală). Efecte favorabile au fost obținute și cu niacină și evolocumab, dar nu de aceeași amploare. Cuantificăm riscul inflamator fie prin intermediul markerilor indirecti, cum ar fi CRPhs, dar și prin inducerea, în asocieri cu limfocokinele, a modificării endoteliale, fie direct, prin dozarea markerilor mai fiabili - Interleukina 1 și 6 și interleukina 8 și MCP 1 mai precoce, apoi TNF α , interferon β 1, molecule solubile de aderență vasculară (VCAM-1), fosfolipaza A2 asociată cu lipoproteinele circulante (FLPA2), IGF-1 (Insulin Like Growth Factor-1), molecule solubile de Selectin-E și -P, produse finale de glicaj (PFG), nivelul sanguin de NO și conținutul seric crescut de peroxinitrit (ONOO-), produsul de interacțiune dintre NO și anionul superoxid. Mai multe studii au evaluat efectul colchicinei la pacienții cu boală coronariană ischemică. Medicamentul previne polimerizarea microtubulilor prin interferența cu funcția leucocitelor. Studiile LODOCO II, COLCOT, CLEAR16, doar ultimul neconcludent pentru efectul profilactic al colchicinei. Studii cu inhibitori de interleukină/inhibitori de chemokine, CANTOS - cu canakinumab, Virginia Commonwealth University Anakinra Remodelling Trial 38, cu anakinra, RESCUE, cu Ziltivekimab. Medicamentele non-antiinflamatoare primare, statinele, inhibitorii de proproteine convertesc subtilisina/kexina de tip 9 (PCSK9), agonistii GLP1, terapiile mici și interferente bazate pe ARN, adăugarea și editarea genelor (CRISPR), inclusiv repetările palindromice scurte grupate în mod regulat și editarea bazelor sunt surse de speranță. Întrebarea majoră, în ciuda problemelor economice actuale, este: nu ar fi eficiente terapiile antiinflamatorii endoteliale sistemice (nu neapărat cele deja testate), la pacienții cu risc ridicat și cu dovezi de inflamație, în profilaxia primară? Nu s-au făcut astfel de studii, cel puțin nu studii randomizate, în loturi semnificative, deocamdată. Profilaxia primară este, în secolul XXI, evident, o altă etapă de concept și dezvoltare a terapiei nu numai pentru salvare de viață, pentru durată de viață ci și pentru o viață sănătoasă a populației.

Cuvinte cheie

Ateroscleroză/aterotromboză, placă „vulnerabilă”, risc inflamator rezidual, tratamente hipolipemiente, tratamente antiinflamatorii endoteliale primare, terapii non-antiinflamatorii primare, studii de prevenție aterotrombotică secundară cu antiinflamatoare

Introduction

Due to multiple risk factors, recent decades have shown atherothrombotic pathology to be the most formidable enemy of human health and lifespan in the modern world. Important advances have been reported in the field through the physiological and morphopathological knowledge of the phenomenon, but also through new therapies. Among these are the lipid-lowering and implicitly anti-inflammatory therapies with pleiotropic effects - mainly statins, but also new formulas; monoclonal antibodies, especially alirocumab and evolocumab; PCSK9 inhibitors; siRNA; and PCSK9 receptor blockers, including open series of inclisiran. These have demonstrated possible effects on lipid factors that are less commonly targeted at present, but also very clearly involved in the specified pathological process - including lipoprotein(a) and apolipoprotein B - but also an insufficient ability to adequately decrease the atherosclerotic and implicitly atherothrombotic risk. The so-called “residual risk” is implicated in arterial endothelial ischemic recurrences in all vascular territories - a risk that is today considered exclusively inflammatory. There have been morphological, physiopathological, and biochemical advances in our understanding. We have an improved understanding of not only the genetically-determined phenomenology of atherosclerosis, but also the development of various means of reperfusion - (i.e., preserving a vascular caliber strictly in the large or medium vascular territories, such as the epicardial coronary arteries, and less in the microvascular territories). This has led to the accentuation of an unwanted endothelial response to barotrauma and “foreign bodies,”

even in the presence of pharmacologically active antiproliferative devices (stents). Endothelial inflammation, whether native and genetically determined or caused by the biological behavior of the patient, has become more and more evident in large-population studies and in randomized, multicenter studies, beyond the apparent control of classic risk factors.

Reviewing the present data in the literature

Inflammation of the endothelium (originating in situ or exogenous) has been attributed to general inflammatory diseases (including autoimmune diseases, which can be accelerated by the conditions for the development of a true inflammation); hypertension (caused by the hyperexpression of angiotensin 2, which is a trigger of endothelial inflammation); dyslipidemia (caused by LDL cholesterol in small, dense and oxidized fractions); hyperapolipoprotein B or increase in lipoprotein(a); hypertriglyceridemia and hypoHDL, which are often associated with one another as in atherogenic dyslipidemia from diabetes; and dysglycemia, more specifically hyperglycemic spikes. Hyperinsulinism has also been implicated in accelerating endothelial inflammation, especially in middle age (39-56 years).^{1,4,16}

Newer data, based not only on genetic information, but also on morphological studies and new markers of endothelial inflammation (in this case, the reaction of lymphocytokines, including the reaction

of blood components such as lympho-monocytes, but also blood platelets), can contribute to the precipitation of atherothrombotic phenomena with a predominantly inflammatory prothrombotic mechanism. Our understanding of atherosclerosis, for example, has a common history with that of oncogenesis, and was described by Otto Heinrich Warburg with exceptional intuition.³ This explains the prophylactic effect of aspirin on some types of cancers, and a more recent observation that has highlighted the effects of aspirin on the risk of metastasis.³

How “vulnerable plaque” forms, the relevance of genetics, and the influence of inflammation on acquired endothelial dysfunction have also been topics of study.¹⁰

In the MESA cohort, for example, which consisted of adults without clinical CVD and cancer at baseline, higher baseline levels of hs-cTnT and NT-proBNP were associated with a higher incidence of cancers over a follow-up period of 17.8 years. These results suggest that hs-cTnT and NT-proBNP levels are not only indicative of the risk of cardiac events and mortality in cancer patients, but also predictive of future cancer risk in people with subclinical CVD.⁵

Of course, the current antithrombotic therapies have also changed the profile of contemporary atherothrombotic disease. Together with the lipid-lowering therapies, they have ushered in a new morphological paradigm for the structure of atheroma plaque, from the “warm” vulnerable plaque, which has a core rich in lipids and is prone to dissection and hemorrhage with consecutive thrombosis, to the “cold” fibrous plaque, which is prone to erosion and distal embolization of fibrocalcereous material.^{4,10} First aspirin, then more potent treatments, such as inhibitors of P2Y₁₂ protein receptors – or, more recently, the association of X-activated antifactor in vascular dosage with aspirin – have shown notable results in studies, but this has exclusively been in anti-atherosclerotic and atherothrombotic secondary prophylaxis. We do not have valid data regarding primary prophylaxis with these treatments.

As we have previously mentioned, neither has the current lipid-lowering therapy provided complete protection, not even in secondary prophylaxis. Using the maximum tolerated doses of potent statins + ezetimibe +/- bempedoic acid – the therapies specified above – we will be able to see, in the near future, the adequacy of some of these therapies for the control of lipoprotein(a) and apolipoprotein B values, which statistically have proven to be even stronger ischemic risk factors than LDL cholesterol and, especially, non-HDL cholesterol.²

In addition to lipidomics, proteomics can also determine the risk of atherosclerotic inflammation, as has recently been reported by mass spectrometry, aptamer assay, etc.¹¹ Many different lipid fractions and their control do not appear in prevention guidelines today, and this is likely to prove unjustified. These include antisense oligonucleotides (ASOs) and small-interfering RNA (siRNA). There are also agents still in the investigation stage. These include pelacarsen (ASO), which is in phase 3 investigation and reduced Lp(a) by 80% at the highest dose; olpasiran (siRNA), which is in phase 3 investigation and showed a profound and sustained reduction in Lp(a); cerlasiran (siRNA), which is in early trial investigation and demonstrated long-lasting Lp(a) suppression for

over 201 days; lepodisiran (siRNA), another promising candidate with sustained Lp(a) reduction for nearly a year; and muvalaplin (oral therapy), which has achieved ~80% Lp(a) reduction by preventing Lp(a) particle formation.

Favorable effects were also achieved with niacin and evolcumab, but not of the same magnitude.⁷

Lipoprotein(a) is implicated in residual inflammatory risk by involving chemokines/cytokines, adhesion molecules, macrophage activation, and monocyte migration.

Today we can quantify the inflammatory risk in the case of atherosclerotic and atherothrombotic pathology either by means of indirect markers, such as CRPhs (a result of inflammatory damage), but also by inducing endothelial alteration in association with lymphocytokines. It does not, however, represent an aggressor lymphocytokine, being somewhat slower in growth and more prompt in self-resolution after the major ischemic-necrotic event. Endothelial alteration can also be induced directly by repetitive dosing of even more reliable markers – interleukin 1 and 6, and earlier interleukin 8 and MCP 1, then TNF α ; soluble vascular adhesion molecules (VCAM-1); phospholipase A₂, which is associated with circulating lipoproteins (FLPA₂); IGF-1 (insulin-like growth factor-1); soluble molecules of selectin-E and -P; glycation end products (PFG); and blood levels of NO and increases in serum content of peroxynitrite (ONOO⁻), which is the interaction product between NO and the superoxide anion.^{8,9} Anti-CXCR3 aAbs is also a recently discovered reliable marker of atherosclerotic risk.¹²

Early markers of inflammatory endothelial suffering – or other, later ones associated with those of ischemic myocardial suffering – lead to a much more accurate and coherent paraclinical diagnosis of inflammation, and a more reliable prophylaxis for new major cardiovascular events.

Not only that, today genetic markers can designate candidates for endothelial inflammation. For example, the mononucleotide polymorphism rs10754555, in an intronic region of the NLRP3 gene, is associated with increased levels of NLRP3 mRNA, and, in turn, with increased systemic inflammation and a higher risk of cardiovascular disease in people under 60 years of age.

Of course, the epigenetics of the individual also has a major impact on the evolution of atherosclerosis. The initiation, extent and progression of subclinical atherosclerosis in otherwise asymptomatic, middle-aged people are linked to the acceleration of the Grim epigenetic age.¹³ Analysis using transcriptomic and proteomic data suggests that systemic inflammation plays an important role in this association, underscoring the need for inflammation control in the prevention of cardiovascular disease. In this case, the pro-inflammatory pathways implicated in the production and extent of the inflammation are IL6, inflammasome, and IL10, and associated genes, including IL1B, OSM, TLR5, and CD14.

The vast majority of clinical trials using both old and new anti-inflammatory drugs in the secondary prophylaxis of new ischemic events, based on knowledge of the impact of endothelial and myocardial inflammation, have confirmed these drugs' significant prophylactic effects.

Colchicine

Several studies have evaluated the effect of colchicine in patients with coronary ischemic disease. This drug prevents the polymerization of microtubules by interfering with the function of leukocytes.^{1,15}

The LODOCO II study evaluated the use of 0.5 mg of colchicine in patients with chronic coronary syndrome in a randomized trial in 5,522 patients. The primary endpoint of the study, evaluated at two years, was a composite of cardiovascular death, spontaneous infarction, ischemic stroke, and coronary revascularization. This primary endpoint was documented in 6.8% of patients in the colchicine group and 9.6% of patients in the placebo group (risk ratio [RR]: 0.69; CI: 0.57-0.83; $P < 0.001$). The incidence of cardiovascular death or the myocardial infarction endpoint was also significantly reduced with colchicine (1.3% vs. 1.8%, respectively; RR: 0.71; $P = 0.001$). There were no differences in hospitalizations for infection, including pneumonia or gastrointestinal disorders.

In the randomized COLCOT trial, colchicine was tested in 4,745 patients with recent prior myocardial infarction (within the last 30 days). The primary endpoint (composite of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, stroke, and hospitalization for angina) occurred in 5.5% of patients treated with colchicine, compared to 7.1% of subjects in the placebo group (RR: 0.77; CI: 0.61-0.96; $P = 0.02$). The HR was 0.84 for cardiovascular death and 0.91 for myocardial infarction.

It was for this reason – as evidenced by the recent guidelines from the European Society of Cardiology that suggested the use of the drug in ischemic heart disease with improvements from class II B to II A – that the CLEAR16 study, which tested colchicine in ACS, was initiated. CLEAR16 was the first clinical trial to test the superiority of colchicine over placebo in subjects with ACS. It was a multicenter, randomized, double-blind study of 795 patients with 12-month UF. Colchicine was administered at a dose of 0.5 mg, twice a day, for the first month, and then at 0.5 mg/day thereafter. The primary endpoint of the study – a composite of cardiovascular death, myocardial infarction recurrence, stroke, or revascularization, assessed three years after enrollment – was found in 9.1% of patients in the colchicine group and 9.3% of patients in the placebo group (RR: 0.99; CI: 0.85-1.16; $P = 0.93$). There was no downward trend at UF for any individual endpoint. The RR was 1.03 for cardiac death, 0.88 for infarction recurrence, 1.15 for stroke, and 1.01 for revascularization.

The data presented are difficult to interpret because they differ significantly from other studies. The different selection of patients in the CLEAR study (STEMI) compared to the COLCOT and LODOCO studies does not seem to be a sufficient justification. In a more severe clinical setting, even greater efficacy should have been expected from the use of the anti-inflammatory drug. One objection in colchicine's defense is that the therapy was discontinued in 25% of the subjects.

Interleukin/chemokine inhibitors

In the CANTOS study – a clinical trial in patients with ischemic heart disease – the impact of an anti-IL-1 β human monoclonal antibody was evaluated. The study randomized 10,061 patients with previous myocardial infarction to three different doses of canakinumab (50, 150 and 300 mg) versus placebo. There was a significant reduction in hs-CRP values in the three canakinumab treatment groups compared to the baseline and placebo groups. In addition, in the 150- and 300-mg-canakinumab groups, there was a significant reduction in the primary endpoint (two-year composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death) compared to the placebo group. The combination of the two canakinumab groups (150 and 300 mg) saw a 15% reduction in the relative risk of achieving the primary endpoint. However, the significant decrease in cardiovascular events came at the expense of an increase in fatal infections.

Virginia Commonwealth University-anakinra remodeling trial 38 was a randomized clinical trial that tested an IL-1 receptor inhibitor. The study included 99 patients with STEMI myocardial infarction. Anakinra significantly reduced hs-CRP levels and the incidence of death or heart failure with new onset compared to placebo (9.4% vs. 25.7%; $P = 0.046$ and 0% vs. 11.4%; $P = 0.011$). An increased incidence of serious infections in the Anakinra arm was not observed.

The RESCUE study tested ziltivekimab, a new human antibody directed against the IL-6 ligand, in its ability to reduce inflammation in patients with advanced chronic kidney disease. The randomized trial was conducted on 264 patients with moderate to severe chronic kidney disease and elevated HSCRP-HS levels (>2 mg/L). At 12 weeks, hs-CRP values were reduced by 77% for the 7.5-mg group, 88% for the 15-mg group, and 92% for the 30-mg group, compared to 4% for the placebo group. The drug was well-tolerated, in the absence of significant side effects. The results of preliminary studies with anakinra and ziltivekimab, as well as with other monoclonal antibodies against IL-6 receptors (tocilizumab and sarilumab), have certainly been encouraging.

Drugs with predominantly non-anti-inflammatory action

Statins are drugs with marked anti-inflammatory and lipid-lowering action. The anti-inflammatory action manifests itself together with the LDL-C-lowering action and can also be a consequence of it. However, this class of drugs, especially in maximum doses, has a pleiotropic action that consists of attenuating the activation of T cells and inhibiting the secretion of proinflammatory cytokines.

Proprotein converting subtilisin/kexin type 9 (PCSK9) inhibitors also exert an anti-inflammatory action that does not appear to be accompanied by reductions in hs-CRP. Indeed, regression studies show a reduction in the inflammatory component, specifically the macrophage content in OCT.¹⁴

GLP1 agonists also exert a significant anti-inflammatory function, decreasing the adhesion of monocytes and the accumulation of macrophages in the plaque. The efficacy of semaglutide that was demonstrated in the SELECT study in obese patients appears to be caused by anti-inflammatory action, as documented by the decrease in hsCRP. It could be related to the significant reduction in perivisceral fat, as well as the pleiotropic action of the drug.^{17,18}

Other molecules that act on different pathways, such as ox-LDL antibodies, 5-lipoxygenase inhibitors and phospholipase A2 inhibitors, were also tested. So far, these drugs have not provided encouraging results.

Measuring inflammation using a systemic index (hsCRP) is a reasonable approach. However, other blood parameters, such as IL-6, can improve accuracy in diagnosing inflammation. Non-invasive CT or CT-PET imaging methods will be able to better identify coronary endothelial inflammation. In therapies that address inflammation as a secondary route of prevention, the utility of statins and PCSK9 inhibitors in reducing inflammation and lowering cholesterol cannot be disputed. There are still no drugs with anti-inflammatory action that have been proven to be effective and safe. The results of studies with colchicine do not go in any one particular direction, especially with side effects that cannot be neglected.

Molecules that inhibit IL-6 are, however, of interest. They could improve the prognosis of patients optimally treated with hypolipidemic therapy, but with certified residual inflammation. Economic problems cannot be neglected either. It could be advantageous to use therapeutic solutions with small interfering RNA, which can greatly reduce the inflammatory component and lower cholesterolemia at the same time.

Small and interfering RNA-based therapies, as well as gene addition and editing (CRISPR), including regularly clustered short palindromic repeats and base editing, have been highlighted for their potential to provide treatments that go beyond even the adherence challenge.¹⁹

REFERENCES

1. Prati F, Mastroianni F, Paoletti G, Marco V, Biccirè FG, Gatto L. Seeking and treating inflammation in ischaemic heart disease: Are we ready? *Eur Heart J Suppl* 2025; 27(Suppl 3):iii122–iii25.
2. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2024;45(36):3415–3537.
3. Liuzzo G, Patrono C. Weekly Journal Scan: Platelet thromboxane suppression as the mechanism of the anti-metastatic effect of aspirin. *Eur Heart J* 2025;46:2356–2358.
4. Bay B, Tanner R, Gao M, Oliva A, Sartori S, Vogel B, Gitto M, Smith KF, Di Muro FM, Hooda A. Residual cholesterol and inflammatory risk in statin-treated patients undergoing percutaneous coronary intervention. *Eur Heart J* 2025;46(32):3167–3177.
5. Cai X, White Q, Johnson WC, Hansen SL, Dardari ZA, Blaha M, Michos ED, Lima JAC, deFilippi CR, Budoff MJ, Watson KE, McClelland RL, Yang EH. Baseline cardiac biomarker levels as predictors of cancer risk in the MESA cohort. *JACC Adv* 2025;4(7):101884.
6. Farukhi ZM, Mora S. Lipoprotein(a) association with residual risk: what has inflammation got to do with it? *Eur Heart J* 2024;45(12):1055–1057.

The major question that can be asked today, despite the current economic problems, is: Wouldn't systemic endothelial anti-inflammatory therapies (not necessarily the ones currently being tested) in high-risk patients with evidence of inflammation be effective in primary prophylaxis? For now, no such studies have been done, at least not serious, randomized, large-scale trials.

Primary prophylaxis is, in the 21st century, another stage in the conceptualization and development of life-saving therapies – not only to extend life, but also for the health of the population. It remains a subject in full development and fundamental research, and only then population.

Conflict of interests

none to declare.

Author Contributions

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7. Vinci P, Di Girolamo FG, Panizon E, Tosoni LM, Cerrato C, Pellicori F, Altamura N, Pirulli A, Zaccari M, Biasinutto C, et al. Lipoprotein(a) as a risk factor for cardiovascular diseases: pathophysiology and treatment perspectives. *Int J Environ Res Public Health* 2023;20(18):6721. doi:10.3390/ijerph20186721.
8. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J* 2022;43(39):3925–3946.
9. Schmidt LE, Speidl WS, Tsimikas S, Mayr M. Reducing reductionism: addressing risk for atherosclerotic cardiovascular disease by apolipoprotein proteomics. *Eur Heart J* 2023;44(27):2420–2422.
10. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. *Eur Heart J* 2015;36(43):2984–2987.
11. Nurmohamed NS, Kraaijenhof JM, Mayr M, Nicholls SJ, Koenig W, Catapano AL, Stroes ESG. Proteomics and lipidomics in atherosclerotic cardiovascular disease risk prediction. *Eur Heart J* 2023;44(18):1594–1607.
12. Müller FS, Aherrahrou R, Grasshoff H, Heidorn MW, Humrich JY, Johanson L, Aherrahrou R, Reinberger T, Schulz A, ten Cate V, et al. Autoantibodies against the chemokine receptor 3 predict cardiovascular risk. *Eur Heart J* 2023;44(47):4935–4949.

13. Sánchez-Cabo F, Fuster V, Silla-Castro JC, González G, Lorenzo Vivas E, Alvarez R, Callejas S, Benguría A, Gil E, Núñez E, et al. Subclinical atherosclerosis and accelerated epigenetic age mediated by inflammation: a multi-omics study. *Eur Heart J* 2023;44(29):2698–2709.
14. Engebretsen I, Ødegaard KM, Halvorsen S, Bugge C, Kristiansen IS, Størring H, Munkhaugen J. Treatment with PCSK9 monoclonal antibodies is associated with discontinuation of oral lipid lowering therapy. *Eur Heart J* 2024; doi:10.1093/ehjqcco/qcae099.
15. Nidorf SM, Ben-Chetrit E, Ridker PM. Low-dose colchicine for atherosclerosis: long-term safety. *Eur Heart J* 2024;45(18):1596–1601.
16. Kosmas CE, Bousvarou MD, Guzman E. Insulin resistance and cardiovascular disease. *SAGE Journals* 2023; first published online Mar 30, 2023.
17. Pedicino D, Volpe M. Weekly Journal Scan: a large observational study unravels the wide-ranging effects of glucagonlike peptide-1 receptor agonists. *Eur Heart J* 2025;46:2713–2715.
18. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;389(24):2221–2232.
19. Gurevitz C, Bajaj A, Khera AV, Do R, Schunkert H, Musunuru K, Rosenson RS. Gene therapy and genome editing for lipoprotein disorders. *Eur Heart J* 2025;00:1–14.