Review

Inflammation and atherosclerotic cardiovascular disease: lights and shadows

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ABSTRACT

Atherosclerosis as an inflammatory process has been a Leitmotiv in cardiology for the past 30 years, and the hypothesis of a causal role has now been tested in several clinical trials aimed at demonstrating that drugs that primarily target inflammation can reduce cardiovascular events. Inflammation indeed drives all phases of atherosclerosis, from inception, through progression, and ultimately acute thrombotic complications triggered by plaque rupture and plaque erosion. Since atherothrombosis causes most acute myocardial ischaemic syndromes, appropriate anti-inflammatory treatments should limit the occurrence of such events and, consequently, of cardiovascular death. Such treatments might also reduce the propensity to thrombosis once the trigger (plaque rupture or erosion) has occurred.

This brief review will summarise the main concepts, initial results and current expectations in this rapidly evolving area of cardiology, borrowing concepts and drugs from immunology and rheumatology. This is an extremely attractive, but still incomplete story, with still many challenges and shadows.

Introduction

Historical remarks and cellular biology mechanisms unravelled

The hypothesis that inflammation drives atherosclerosis and its thrombotic complications (atherothrombosis) has gained considerable credit in cardiovascular medicine in recent times but is not new. Indeed, the famous Berliner pathologist Rudolf Ludwig Karl Virchow (1821-1902) (Fig. 1) wrote:

"In some, particularly violent cases the softening manifests itself even in the arteries not as the consequence of a really fatty process, but as a direct product of inflammation". … "atherosclerosis… is an active process of tissue reaction rather than a mere encrustation of thrombus or deposition of fatty material: "the frequency with which cells in a state of fatty degeneration are found in inflamed parts affords sufficient proof that in the course of inflammatory processes, which we should never regard as simply passive processes, such transformations must take place" (1).

Fig. 1. Rudolf Ludwig Carl Virchow (1821-1902), circa 1893. German physician, anthropologist, pathologist, prehistorian, biologist, writer, editor and politician, known for his advancement of public health. From the 2e collection (Felix Potin, c1893). Artist unknown.
(Photo by The Print Collector/Getty Images).

Virchow is mostly quoted for his characterisation of acute inflammation in tissues, which he described as the passing of neutrophils, normally confined within the flowing blood, into inflamed tissues. More in general, however, the passing of other white blood cells from blood to tissues also occurs in immunological processes (2), as well as in atherosclerosis (3).

While leukocytes do not adhere to a normal endothelium, they do so in the

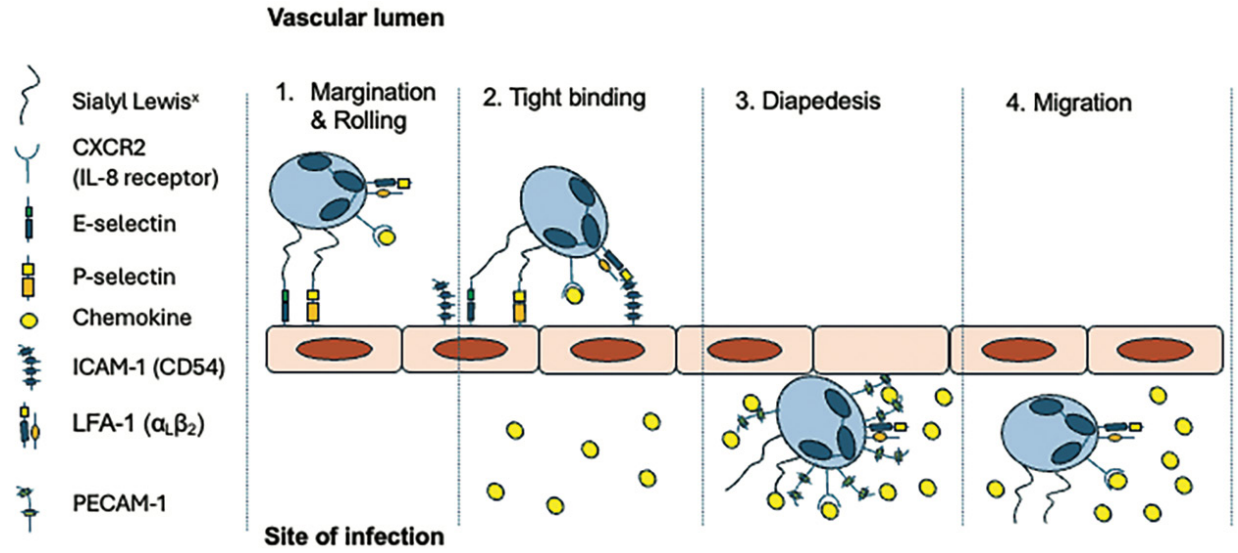

Fig. 2. Cellular and molecular mechanisms of acute inflammation, such as occurring at a site of infection.
Polymorphonuclear leukocyte, normally flowing in blood, are first marginated and forced to roll through the expression of E-selectin and P-selectin on the surface of the activated endothelium, engaging constitutively expressed Sialyl Lewisx carbohydrate ligands on the leukocyte, with an accessory role of chemokines, such as interleukin (IL)-8 engaging the chemokine receptor CXCR2. The polymorphonuclear cell is then forced to a tight binding to the endothelial cells through the engagement of intercellular adhesion molecule-1 (ICAM-1) expressed on the activated endothelium, engaging the integrin Lymphocyte Function-associated Antigen-1 (LFA.1), also known as $\alpha_L\beta_2$. The polymorphonuclear leukocyte then passes through the endothelial cell junctions (diapedesis) in a process of chemoattraction mostly mediated by IL-8 and its CXCR2 ligand, as well as Platelet Endothelial Cell Adhesion Molecule-1. (PECAM-1), followed by migration through a chemokine gradient. The process here depicted in molecular details pertains to acute inflammation, as morphologically described by Virchow in the 19th century. Similar processes, albeit through different mediators, occur in early phases of atherosclerosis, where the protagonist cell is the monocyte, then becoming a macrophage when in the arterial intima, eventually becoming a foam cell, typical of the early atherosclerotic lesion – the so-called fatty streak; as well as in cellular immunity, whereby lymphocytes migrate from the lymph in the lymphnode sinuses to the lymphnode medulla.

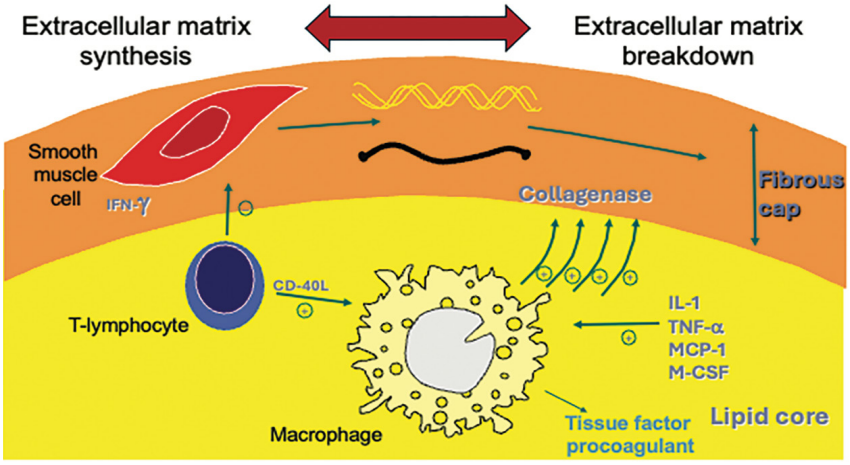

Fig. 3. Inflammation as a driver of plaque rupture.
Plaque rupture is promoted by a weakening of the fibrous cap, made up of collagen, separating the thrombogenic lipid core of the plaque from the flowing blood. The thickness of the fibrous cap depends on the balance between collagen synthesis by smooth muscle cells, and collagen breakdown through the action of collagenases and other matrix metalloproteinases, mostly synthesised by activated macrophages in the lipid core, with an accessory role also played by T-lymphocytes secreting interferon (IFN) gamma (IFN), which inhibits the production of collagen by smooth muscle cells, or CD-40 ligand (CD-40L), promoting the activation of macrophages. Several cytokines, including interleukin (IL)-1, tumour necrosis factor (TNF)-alpha, macrophage chemoattractant protein (MCP)-1 and macrophage-colony stimulating factor (M-CSF) also favour macrophage activation. Modified after (42).

presence of an 'activated' endothelium, a multifaceted process associated with multiple phenotypic changes compared with normal, 'resting' endothelium (4). Cellular and molecular details of these sequential events have been unraveled in a large series of studies in the 1990s. Specific adhesion molecules are expressed on the surface of activated endothelial cells in any type of inflammation, mediating the processes of leukocyte adhesion and transmigration in the intima. At the same time, an array of pro-inflammatory mediators are expressed, that coordinate the homing of leukocytes. Ultimately, the activation of all cells involved, both endothelial cells and leukocytes, provide traffic signals for leukocyte homing (2, 3). Molecules mainly involved in such signaling events are endothelial leukocyte adhesion molecules and chemoattractants.

Neutrophils (polymorphonuclear leukocytes) are the protagonist cells in acute inflammation (Fig. 2). In early stages of atherosclerosis, the protagonist cells are, however, blood monocytes (3). Endothelial leukocyte adhesion molecules involved specifically in atherogenesis belong to the Selectin, the Integrin family, and to a sub-group of the Immunoglobulin superfamily (5) (Table I). P-selectin and E-selectin, by binding to carbohydrate structures as their ligands, mediate "rolling" or transient labile contact of leucocytes with the endothelium. P-selectin, found in endothelial cells overlying human ath-

Table I. Selected endothelial leukocyte adhesion molecules, endothelial chemoattractants and their cognate ligands implicated in atherosclerosis.

Gene family		Molecules/CD nomenclature	Cellular/tissue expression	Cognate ligand
Surface associated				
Integrins	beta2	CD11a/CD18 (LFA-1)	Leukocytes (monocyte, lymphocyte)	ICAM-1,-2 and -3
		CD11b/CD18 (Mac-1)	Leukocytes (monocyte)	
		CD11c/CD18	Leukocytes (monocyte)	
	beta1	a4b1 (VLA-4)	Leukocytes (monocyte, lymphocyte)	
Selectins		L-selectin (CD62L)	Leukocytes	Sialyl Lewis^x and Lewis^a
		E-selectin (ELAM-1, CD62E)	Endothelium	Sialyl Lewis^x and Lewis^a
		P-selectin (CD62P, PADGEM)	Endothelium, platelets	PSGL-1, Sialyl Lewis^x and Lewis^a
Immunoglobulins		ICAM-1	Endothelium and certain leukocyte cell lines	LFA-1 and MAC-1
		ICAM-2	Endothelium, platelets	LFA-1 and Mac-1
		ICAM-3	Leukocytes	
		VCAM-1	Endothelium, smooth muscle	VLA4
		PECAM-1 (CD31)	Endothelium, platelets, leukocytes	
Mucin-like		PSGL-1	Leukocytes	P-selectin
Secreted				
	Cytokine	IL-1	Monocytes, smooth muscle	IL-1 receptor
		TNF	Monocytes, smooth muscle	TNF receptor
		MCP-1	Endothelium smooth muscle	MCP-1 receptor
		M-CSF	Endothelium smooth muscle	M-CSF receptor
	Lipid	PAF	Endothelium, leukocytes	PAF receptor

ELAM: endothelial leukocyte adhesion molecule; ICAM: intercellular adhesion molecule; IL: interleukin; LFA: leukocyte function-associated antigen; MCP: monocyte chemoattractant protein; M-CSF: macrophage colony stimulating factor; VCAM: vascular cell adhesion molecule; PAF: platelet-activating factor; PECAM: platelet-endothelial cell adhesion molecule; TNF: tumour necrosis factor; VLA: very late activation antigen.

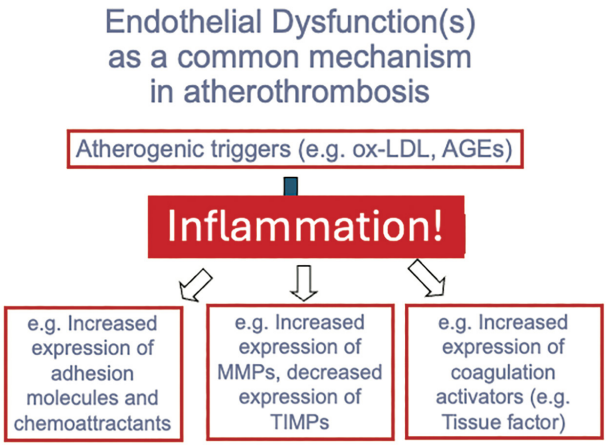

Fig. 4. The central role of endothelial dysfunction(s) and inflammation in vascular disease.
The figure highlights the role of inflammation on endothelial cells, promoting the expression of leukocyte adhesion molecules and chemoattractants in earlier stages of atherosclerosis; promoting plaque complications (plaque rupture and erosion) by a weakening of the fibrous cap; and promoting thrombosis as a complication of plaque rupture/erosion, through the increased expression of tissue factor.
ox-LDL: oxidised low-density lipoproteins; AGEs: advanced glycation endproducts; MMPs: matrix metalloproteinases; TIMPs: tissue inhibitors of metalloproteinases.

eroma (6), is involved in atherogenesis since hyperlipidemic mice lacking P-selectin exhibit slowed-down atheroma formation (7). A more prominent role in atherogenesis is, however, attributed to vascular cell adhesion molecule-1 (VCAM-1), belonging to the immunoglobulin superfamily. VCAM-1 mediates steady adhesion of monocytes to the endothelium by binding to the cognate ligand Very Late Antigen (VLA)-4, which is specifically expressed on the surface of circulating monocytes and T lymphocytes (8). VCAM-1 knock-out mice are embryonic lethal, but models in which only one domain of the protein is genetically deleted, bred with the atherosclerosis-prone low-density lipoprotein receptor *LDLR*$^{-/-}$ mice, show reduced lesion formation (9).

The expression of VCAM-1, as well as of E-selectin and of soluble endothelial products, such as monocyte chemoattractant protein (MCP)-1, macrophage-colony stimulating factor (M-CSF), interleukin (IL)-6 and IL-8 (see below), is induced by pro-inflammatory cytokines such as IL-1 and tumour-necrosis-factor (TNF)-α, which are expressed in atheromata. In turn, IL-1 maturation from a longer protein precursor is effected, through caspase-1, by the NLRP3 (NLR family pyrin domain containing 3) inflammasome, a multiprotein complex that acts as a critical sensor in the innate immune system, detecting cellular stress, pathogens, and danger signals (10). VCAM-1 expression is also induced, through NLRP3 inflammasome activation, by components of oxidised lipoproteins, such as oxidised phospholipids and short chain

aldehydes (11, 12), and by advanced glycation endproducts (13), providing a good mechanistic explanation for the action of common cardiovascular risk factors. Common to all these signaling pathways is the increased transcription of a variety of genes of endothelial activation through the activation of the transcription factor nuclear factor (NF)-κB. NF-κB thus represents a common pathway that can coordinate the expression of a number of genes involved in endothelial activation (14).

Inflammation is, however, also involved in subsequent stages of atheroma evolution and complications triggered by plaque rupture or by plaque erosion (15). Inflammatory activation, involving multiple components of innate or acquired immunity 16, predisposes plaques to such acute complications (17), by acting through the activation of matrix metalloproteinases, as well as inhibiting collagen synthesis, through a weakening of the fibrous cap, separating the thrombogenic lipid core from the flowing blood. In addition, inflammatory cytokines induce the expression of tissue factor in endothelial cells, promoting thrombogenesis. These mechanisms have been revised in detail in (4), and illustrated in Figure 3. In essence, inflammation appears as a common theme characterising all the evolution of vascular disease (Fig. 4).

All this provides a solid foundation for the hypothesis that inflammation can also be a target for specific interventions.

From mechanistic hypotheses to a clinical readout

The clinical applicability of the concept of inflammation in vascular disease can be traced back, among others, to two leading investigators, Attilio Maseri (Fig. 5) and Paul M. Ridker (Fig. 6). In 1994, Maseri's group reported that two circulating markers of inflammation, C-reactive protein (CRP) and serum amyloid A protein were elevated in severe unstable angina (most of which we would now term non-ST elevation myocardial infarction), and had important prognostic information, as patients with higher levels (≥0.3 mg/dL on admission) had a higher rate of evolution towards overt myocardial infarction or death (18). CRP is produced by the liver in response mainly to IL-6, and is a stable, easy-to-measure acute-phase reactant able to report, when measured with sufficiently sensitive assays, about even low-grade systemic inflammation. In a number of subsequent report, Ridker *et al*. convincingly reported that CRP, measured with a high-sensitivity assay (high-sensitivity CRP, hsCRP) was elevated years before an acute myocardial infarction, and its levels had a concentration-dependent prognostic value in subjects without evidence of vascular disease (19); may be useful to prompt statin therapy in primary prevention even in subjects with low LDL cholesterol (20); predicts vascular events at least as LDL-cholesterol (21); and predicts cardiovascular events additive to cholesterol and also in patients receiving statin therapy (22).

This research line has led to the idea of concentrating attempts at targeting atherosclerotic cardiovascular disease to subjects with high levels of CRP.

Fig. 5. Attilio Maseri (1935-2021).
Italian cardiologist, promoter of the concept of inflammation in acute coronary syndromes.

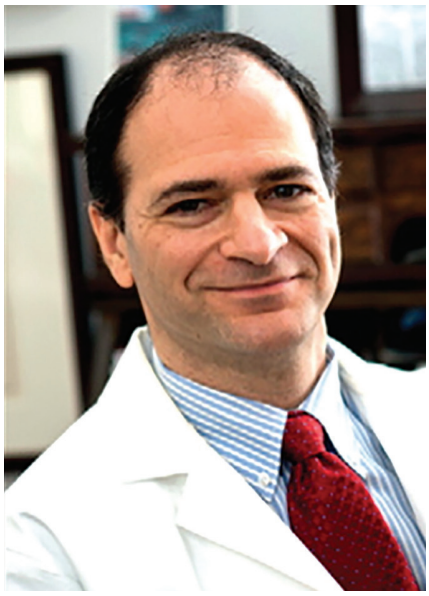

Fig. 6. Paul M. Ridker.
American scientist, promoter of the use of C-reactive protein as an appropriate marker of inflammation in cardiovascular disease and a way to select patients for adequate trials with anti-inflammatory agents.

Anti-inflammatory therapies and cardiovascular outcomes

The idea of targeting inflammation in cardiovascular disease dates back now many years, with a trial of prednisone in dilated cardiomyopathy (23), with equivocal results. Only in recent years, however, attempts have been directed to atherosclerotic cardiovascular disease. An account of these trials is provided in Table II. Agents used in these trials can be divided into 'specific' and 'non-specific', according to whether inflammation has been targeted independent of other points of action also addressing inflammation, or not. The first 'pure' anti-inflammatory therapy attempted in atherosclerotic cardiovascular disease has been in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial with canakinumab, a monoclonal antibody against IL-1 (24, 25). Here canakinumab dose-dependently reduced the primary endpoint of non-fatal myocardial infarction, nonfatal stroke, or cardiovascular death (main study) (24); and of a composite of heart failure (HF) and HF-related mortality (HF outcomes study) (25). This therapeutic strategy was not, however, further pursued because of an increased risk of infection (24).

Methotrexate, for decades used by rheumatologists and reasonably safe when used at low doses, was then tried in the Cardiovascular Inflammation Reduction Trial (CIRT) trial, but with no reduction in cardiovascular event rates. Methotrexate, however, did not lower IL-1, IL-6, or hsCRP, questioning the unitary concept of 'anti-inflammatory agents', and calling for a deeper understanding of the multiple targets usually grouped under the general term of inflammation.

Table II. Major clinical trials testing anti-inflammatory strategies in cardiovascular disease.

Trial name (acronym)	Drug	Sample size (n)	Population/NYHA Functional Class	Follow-up	Primary endpoint	Treatment outcome
ATTACH (29)	Infliximab (TNF inhibitor)	150	NYHA III	7 mo	Clinical status (composite score) at 14 weeks	No improvement or worsening (with high doses) of clinical condition
ACCLAIM (30)	Celacade	2,426	NYHA II-IV HF	10.2 mo	Composite: all-cause mortality and CV hospitalisation	No difference in primary endpoint; improved outcomes in subjects with prior MI and NYHA II HF
CANTOS (24, 25)	Canakinumab (anti–IL-1)	10,061	Prior MI; hsCRP ≥2 mg/L	3.7 y	Nonfatal MI, nonfatal stroke, or CV death (main study (24) HHF; composite of HF and HF-related mortality (HF outcomes study (25)	Dose-dependent reduction in primary endpoint events
CIRT (31)	Methotrexate	4,786	Previous MI stable CAD	2.3 y (median)	CV event rates	No reduction in CV event rates; did not lower IL-1, IL-6, or hsCRP
CLEAR SYNERGY (32)	Colchicine	3,528	Acute MI plus PCI	3 y	Death from CV causes, recurrent MI, stroke, or unplanned ischaemia-driven coronary revascularisation	Colchicine did not reduce primary endpoint when started soon post-MI
COLCOT (33)	Colchicine	4,745	Stable post-MI patients	22.6 mo	CV event reduction	Significantly lower risk of ischaemic CV events than placebo
CORONA (34)	Rosuvastatin	5,011	NYHA II-IV HF	32.8 mo	Composite of CV death, nonfatal MI, or non-fatal stroke	No difference in primary point; reduction in CV endhospitalisations
GISSI-HF (35)	Rosuvastatin	4,574	NYHA II-IV HF	3.9 y	All-cause mortality; composite of all-cause mortality and CV hospitalisation	No difference in primary endpoint
GISSI-HF (35)	Omega-3 PUFA	6,975	NYHA II-IV HF	3.9 y	All-cause mortality; composite ofall-cause mortality and CV hospitalisation	Modest reduction in all-cause mortality (HR: 0.91; 95% CI: 0.833-0.998), and composite endpoint (HR: 0.92; 99% CI: 0.849-0.999)
JUPITER (36)	Rosuvastatin	17,802	No CVD (LDLcholesterol <130 mg/dL; hsCRP ≥2 mg/L)	1.9 y (median)*	First-ever MI, stroke, hospitalisation for unstable angina, arterial revascularisation, or CV death	Significantly lower risk of CV events than placebo (HR: 0.56; 95% CI: 0.46-0.69)
LoDoCo2 (37)	Colchicine	5,522	Stable ASCVD	28.6 mo	CV event reduction	Significantly lower risk of CV events than placebo
OPT-CHF (38)	Oxypurinol (XO inhibitor)	405	NYHA III-IV HF	6 mo	Composite of HF morbidity, mortality, and quality of life	No difference in primary endpoint; improvement in patients with hyperuricaemia
PREDIMED (39)	Mediterranean diet	7,447	No CVD	4.8 y (median)	Major CVD event: MI, stroke, or death from CV causes	HR for olive oil: 0.69 (95% CI: 0.53-0.91); HR for nuts: 0.72 (95% CI: 0.54-0.95)
Prednisone DCM (23)	Prednisone	102	DCM, NYHA not stated	3 mo	LVEF increase ≥5 percentage points	Small LVEF improvement of limited duration
RENEWAL (40)	Etanercept (TNF inhibitor)	2,048	NYHA II-IV HF	5.7 and 12.9 mo*	Clinical status at 24 wks; combined outcome of death or HHF	No difference in primary endpoints
TIMIC (41)	Prednisone and azathioprine	85	Inflammatory CM, NYHA II-IV	6 mo	LV function changes over 6 mo	Significant improvement in LVEF and decrease in LV volumes

*Terminated early.
ACCLAIM: advanced chronic heart failure clinical assessment of immune modulation therapy; ASCVD: atherosclerotic cardiovascular disease; ATTACH: Anti-TNF Therapy Against Congestive Heart Failure; CAD: coronary artery disease; CANTOS: Canakinumab Antiinflammatory Thrombosis Outcomes Study; CIRT: Cardiovascular Inflammation Reduction Trial; CLEAR-SYNERGY: Colchicine and Spironolactone in Patients With Myocardial Infarction/SYNERGY Stent Registry; CM: cardiomyopathy; COLCOT: Colchicine Cardiovascular Outcomes Trial; CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; CV: cardiovascular; CVD: cardiovascular disease; DCM: dilated cardiomyopathy; GISSI-HF: Gruppo Italiano per lo Studio Della Sopravvivenza Nella Insufficienza Cardiaca-Heart Failure; HF: heart failure; HHF: hospitalisation for heart failure; hsCRP: high-sensitivity C-reactive protein; IL-1: interleukin-1; IL-6: interleukin-6; JUPITER: Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL: low-density lipoprotein; LoDoCo2: low-dose colchicine for secondary prevention of cardiovascular disease 2; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OPT-CHF: oxypurinol therapy for congestive heart failure; PCI: percutaneous coronary intervention; PREDIMED: Prevención con Dieta Mediterránea; Prednisone DCM: prednisone in dilated cardiomyopathy; PUFA: polyunsaturated fatty acid; RENEWAL: Randomized Etanercept Worldwide Evaluation; TIMIC: tailored immunosuppression in inflammatory cardiomyopathy; TNF: tumour necrosis factor; XO: xanthine oxidase.
Colour code: light grey: globally favourable results for the 'anti-inflammatory' therapy tested; dark grey: globally neutral or unfavourable results.

Table III. Ongoing trials of anti-inflammatory therapies in atherosclerotic cardiovascular disease.

Trial	Study design	Population	Intervention	Active comparator	Primary endpoint(s)	Result
Colchicine						
TACTIC, NCT06215989	Randomised, double-blind, placebo-controlled	6574 ACS	Colchicine 0.5 mg/day	Placebo	Cardiovascular death, non-fatal ischaemic stroke, non-fatal spontaneous MI, readmission for ACS, and ischaemia-driven unplanned revascularisation	Expected in 2028
COL-BE PCI NCT06095765	Randomised, double-blind, placebo-controlled	2770 ACS and CCS post-PCI	Colchicine 0.5 mg/day	Placebo	All-cause death, spontaneous (non-procedural) MI, stroke, coronary revascularisation	Expected in 2028
COLCARDIO-ACS, ACTRN12616000400460	Randomised, double-blind, placebo-controlled	3000 ACS with hs-CRP ≥2 mg/L measured 4–52 weeks post-ACS	Colchicine 0.5 mg/day	Placebo	MI, urgent unscheduled revascularisation, cardiovascular death, and non-fatal stroke	Expected in 2029
Ziltivekimab (anti-IL-6)						
ARTEMIS, NCT06118281	Randomised, double-blind, placebo-controlled	10 000 (estimated) NSTEMI/STEMI	Ziltivekimab 30 mg loading dose, then 15 mg/month	Placebo	Cardiovascular death, non-fatal MI, non-fatal stroke	Expected in 2026

ACS: acute coronary syndromes; HR: hazard ratio; hs-CRP: high-sensitive C-reactive protein; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Colchicine, a widely used drug for gout and pericarditis, has been now tested in multiple trials (Table II), with initial apparently favourable results. The most recent Colchicine and Spironolactone in Patients With Myocardial Infarction/ SYNERGY Stent Registry (CLEAR-Synergy) trial has been, however, quite negative, questioning the current indication (Class 2b, Level B-R) for colchicine post-myocardial infarction issued by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (26). Several trials with colchicine are still, however, ongoing (Table III), with expected results within 2029.

IL-6 is also a promising target for anti-inflammatory therapies, such as with the monoclonal antibody ziltivekimab (Table III). Il-6 acts downstream to IL-1, and its targeting may limit some of the unfavourable effects seen with canakinumab in CANTOS.

Conclusions

As one may perceive by the different colours symbolising favourable *versus* dubious results in Table II, the clinical exploitation of the inflammatory hypothesis of atherosclerotic cardiovascular disease with anti-inflammatory agents is still an ongoing story, with some lights and some shadows. Concerns revolve essentially around the possibility that quenching inflammation may limit a vital mechanism of preventing diseases, mostly infectious diseases. The years to come will yield a final proof of the hypothesis, telling whether specific anti-inflammatory agents may be added to the current armamentarium of lipid-lowering and anti-thrombotic agents now well established in our quiver, in addition to lifestyle interventions, to fight cardiovascular disease. Several other promising therapies, such as the omega-3 fatty acid derivative icosapent ethyl, tested in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) in hypertriglyceridemic patients (27), or the glucagon-like peptide-1 receptor agonist (GLP-1 RA), initially designed as antidiabetic agents and now with expanding indications (28), may well fit also the criteria for being cardiovascular 'anti-inflammatory' agents, albeit with specific mechanisms of action indirectly also affecting inflammation.

At the end, the entire concept of "inflammation" will need to be further dissected and eventually seen as an oversimplified term. As Albert Einstein wrote: "*Make everything as simple as possible, but not simpler*", meaning one should try to simplify concepts to their core elements, finding elegant, understandable explanations that still capture the full truth of a complex subject, but avoiding oversimplification or vicious reductionism that distorts reality.

References

1. VIRCHOW R: *Cellular Pathology*. London, UK: John Churchill; 1958.
2. SPRINGER TA: Adhesion receptors of the immune system. *Nature* 1990; 346: 425-34. https://doi.org/10.1038/346425a0
3. GIMBRONE MA, JR., GARCÍA-CARDEÑA G: Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res* 2016; 118(4): 620-36. https://doi.org/10.1161/circresaha.115.306301
4. DE CATERINA R, LIBBY P: *Endothelial Dysfunctions in Vascular Disease*: Wiley-Blackwell; 2008.
5. CARLOS TM, HARLAN JM: Leukocyte-endothelial adhesion molecules. *Blood* 1994; 84: 2068-101.
6. VORA D, FANG Z, LIVA S *et al*.: Induction of P-selectin by oxidized lipoproteins. Separate effects on synthesis and surface expression. *Circ Res* 1997; 80(6): 810-18. https://doi.org/10.1161/01.res.80.6.810
7. DONG Z, CHAPMAN S, BROWN A, FRENETTE P, HYNES R, WAGNER D: The combined role of P- and E-selectins in atherosclerosis. *J Clin Invest* 1998; 102.
8. CYBULSKY M, GIMBRONE MJ: Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science* 1991; 251: 788-91. https://doi.org/10.1126/science.1990440
9. CYBULSKY M, IIYAMA K, LI H *et al*.: A major role for VCAM-1 but not ICAM-1, in early atherosclerosis. *J Clin Invest* 2001; 107(10): 1255-62. https://doi.org/10.1172/jci11871
10. ZOU C, JIANG S, LI H, ZHAO K, CAO D, YANG

G: The NLRP3 inflammasome: mechanisms of activation, regulation, and therapeutic opportunities. *MedComm* (2020) 2026; 7: e70660. https://doi.org/10.1002/mco2.70660
11. BERLINER J, TERRITO M, SEVANIAN A *et al*.: Minimally modified low density lipoprotein stimulates monocyte endothelial interactions. *J Clin Invest* 1990; 85(4): 1260-66. https://doi.org/10.1172/jci114562
12. KUME N, CYBULSKY MI, GIMBRONE MA: Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. *J Clin Invest* 1992; 90(3): 1138-44. https://doi.org/10.1172/jci115932
13. BASTA G, LAZZERINI G, MASSARO M *et al*.: Advanced glycation end products activate endothelium through signal-transduction receptor RAGE: a mechanism for amplification of inflammatory responses. *Circulation* 2002; 105: 816-22. https://doi.org/10.1161/hc0702.104183
14. COLLINS T: Biology of disease: endothelial nuclear factor-kB and the initiation of the atherosclerotic lesion. *Lab Invest* 1993; 88: 499-508.
15. RAMJI DP, DAVIES TS: Cytokines in atherosclerosis: key players in all stages of disease and promising therapeutic targets. *Cytokine Growth Factor Rev* 2015; 26(6): 673-85. https://doi.org/10.1016/j.cytogfr.2015.04.003
16. HANSSON GK, HERMANSSON A: The immune system in atherosclerosis. *Nat Immunol* 2011; 12: 204-12. https://doi.org/10.1038/ni.2001
17. BENTZON JF, OTSUKA F, VIRMANI R, FALK E: Mechanisms of plaque formation and rupture. *Circ Res* 2014; 114(12): 1852-66. https://doi.org/10.1161/circresaha.114.302721
18. LIUZZO G, BIASUCCI LM, GALLIMORE JR *et al*.: The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med* 1994; 331: 417-24. https://doi.org/10.1056/nejm199408183310701
19. RIDKER PM, CUSHMAN M, STAMPFER MJ, TRACY RP, HENNEKENS CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973-79. https://doi.org/10.1056/nejm199704033361401
20. RIDKER PM, RIFAI N, CLEARFIELD M *et al*.: Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344: 1959-65. https://doi.org/10.1056/nejm200106283442601
21. RIDKER PM, HENNEKENS CH, BURING JE, RIFAI N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836-43. https://doi.org/10.1056/nejm200003233421202
22. RIDKER PM, BHATT DL, PRADHAN AD, GLYNN RJ, MACFADYEN JG, NISSEN SE: Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. *Lancet* 2023; 401: 1293-301. https://doi.org/10.1016/s0140-6736(23)00215-5
23. PARRILLO JE, CUNNION RE, EPSTEIN SE *et al*.: A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N Engl J Med* 1989; 321: 1061-68. https://doi.org/10.1056/nejm198910193211601.
24. RIDKER PM, EVERETT BM, THUREN T *et al*.: Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377: 1119-131. https://doi.org/10.1056/nejmoa1707914
25. EVERETT BM, CORNEL JH, LAINSCAK M *et al*.: Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation* 2019;139:1289-1299. https://doi.org/10.1161/circulationaha.118.038010
26. VIRANI SS, NEWBY LK, ARNOLD SV *et al*.: 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2023; 148: e9-e119. https://doi.org/10.1161/cir.0000000000001168
27. BHATT DL, STEG PG, MILLER M *et al*.: Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019; 380: 11-22. https://doi.org/10.1056/nejmoa1812792
28. SALVADOR R, MOUTINHO CG, SOUSA C, VINHA AF, CARVALHO M, MATOS C: Semaglutide as a GLP-1 agonist: a breakthrough in obesity treatment. *Pharmaceuticals* (Basel) 2025; 18. https://doi.org/10.3390/ph18030399
29. CHUNG ES, PACKER M, LO KH, FASANMADE AA, WILLERSON JT: Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003; 107: 3133-40. https://doi.org/10.1161/01.cir.0000077913.60364.d2
30. TORRE-AMIONE G, ANKER SD, BOURGE RC *et al*.:. Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomised trial. *Lancet* 2008; 371: 228-36. https://doi.org/10.1016/s0140-6736(08)60134-8
31. RIDKER PM, EVERETT BM, PRADHAN A *et al*.: Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; 380: 752-62. https://doi.org/10.1056/nejmoa1809798
32. JOLLY SS, D'ENTREMONT MA, LEE SF *et al*.: Colchicine in acute myocardial infarction. *N Engl J Med* 2025; 392: 633-42. https://doi.org/10.1056/nejmoa2405922
33. TARDIF JC, KOUZ S, WATERS DD *et al*.: Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; 381: 2497-505. https://doi.org/10.1056/nejmoa1912388
34. KJEKSHUS J, APETREI E, BARRIOS V *et al*.: Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; 357: 2248-61. https://doi.org/10.1056/nejmoa0706201
35. TAVAZZI L, MAGGIONI AP, MARCHIOLI R *et al*.: Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 1231-39. https://doi.org/10.1016/s0140-6736(08)61240-4
36. RIDKER PM, DANIELSON E, FONSECA FA *et al*.: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195-207. https://doi.org/10.1056/nejmoa0807646
37. NIDORF SM, FIOLET ATL, MOSTERD A *et al*.: Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; 383: 1838-47. https://doi.org/10.1056/nejmoa2021372
38. HARE JM, MANGAL B, BROWN J *et al*.: Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol* 2008; 51: 2301-9. https://doi.org/10.1016/j.jacc.2008.01.068
39. ESTRUCH R, ROS E, SALAS-SALVADÓ J *et al*.: Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018; 378: e34. https://doi.org/10.1056/nejmoa1800389
40. MANN DL, MCMURRAY JJ, PACKER M *et al*.: Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; 109: 1594-602. https://doi.org/10.1161/01.cir.0000124490.27666.b2
41. FRUSTACI A, RUSSO MA, CHIMENTI C: Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009; 30: 1995-2002. https://doi.org/10.1093/eurheartj/ehp249
42. LIBBY P: Molecular bases of the acute coronary syndromes. *Circulation* 1995; 91: 2844-50. https://doi.org/10.1161/01.cir.91.11.2844