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STATE OF THE ART REVIEW
Acute cardiovascular care

Inflammation in acute myocardial infarction: the good, the bad and the ugly

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Abstract

Convergent experimental and clinical evidence have established the pathophysiological importance of pro-inflammatory pathways in coronary artery disease. Notably, the interest in treating inflammation in patients suffering acute myocardial infarction (AMI) is now expanding from its chronic aspects to the acute setting. Few large outcome trials have proven the benefits of anti-inflammatory therapies on cardiovascular outcomes by targeting the residual inflammatory risk (RIR), i.e. the smouldering ember of low-grade inflammation persisting in the late phase after AMI. However, these studies have also taught us about potential risks of anti-inflammatory therapy after AMI, particularly related to impaired host defence. Recently, numerous smaller-scale trials have addressed the concept of targeting a deleterious flare of excessive inflammation in the early phase after AMI. Targeting different pathways and implementing various treatment regimens, those trials have met with varied degrees of success. Promising results have come from those studies intervening early on the interleukin-1 and -6 pathways. Taking lessons from such past research may inform an optimized approach to target post-AMI inflammation, tailored to spare 'The Good' (repair and defence) while treating 'The Bad' (smouldering RIR) and capturing 'The Ugly' (flaming early burst of excess inflammation in the acute phase). Key constituents of such a strategy may read as follows: select patients with large pro-inflammatory burden (i.e. large AMI); initiate treatment early (e.g. ≤12 h post-AMI); implement a precisely targeted anti-inflammatory agent; follow through with a tapering treatment regimen. This approach warrants testing in rigorous clinical trials.

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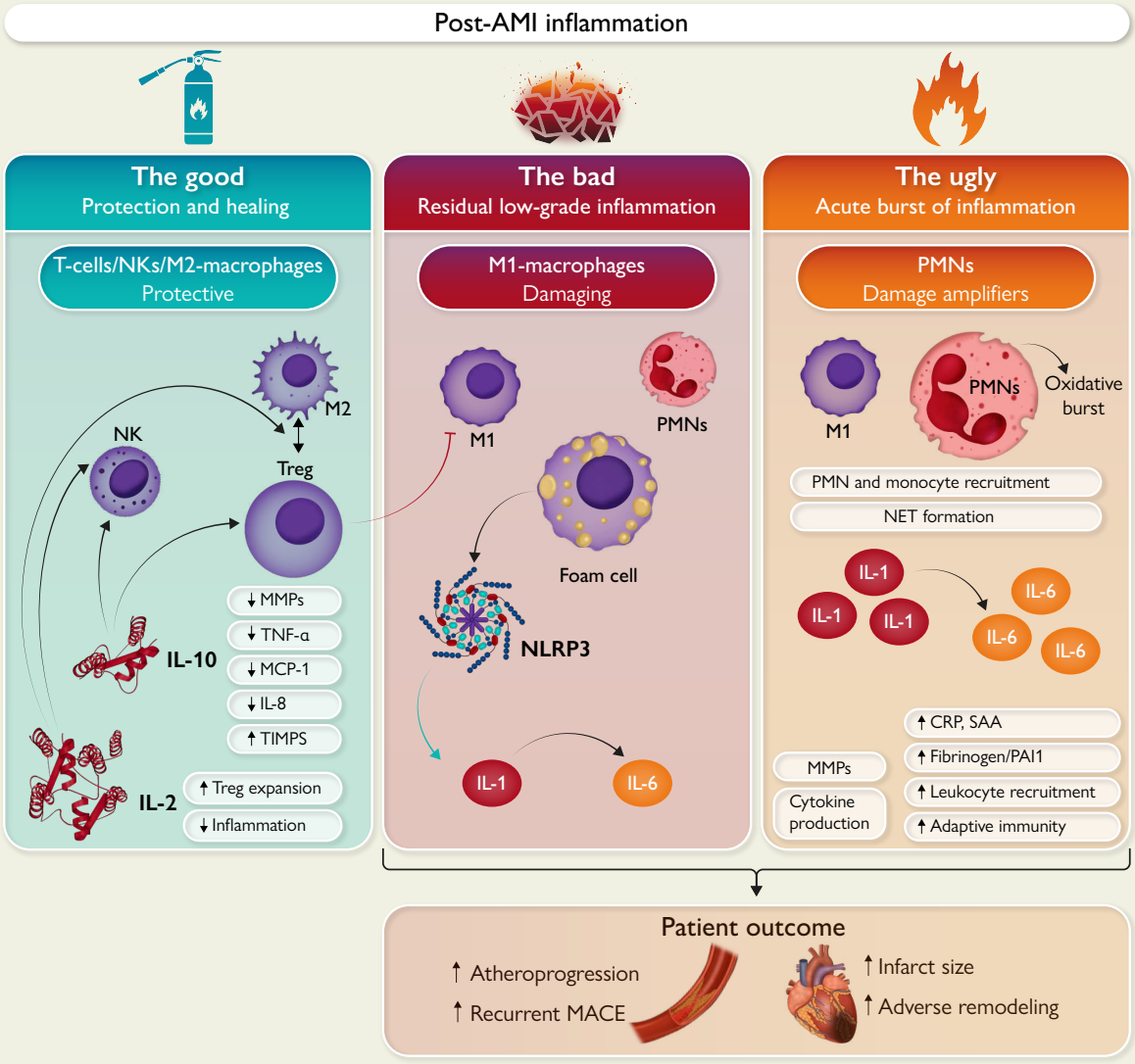
Graphical Abstract



'The Good', 'The Bad', and 'The Ugly': Distinct facets of inflammation in acute myocardial infarction (AMI). The left panel ('The Good') shows the role of cytokines, T-cells, NKs, and macrophages in myocardial protection and healing. IL-10 and IL-2 reduce pro-inflammatory signals (e.g. TNFα, MCP-1, IL-8), extracellular matrix remodelling (MMP downregulation), while promoting Treg, Th2, and NK activation with subsequent macrophage polarization towards the M2 phenotype. The mid panel ('The Bad') represents the smouldering state of low-grade inflammation persisting in the late phase after AMI. Among the protagonist cellular players responsible for 'The Bad' are M1-polarized macrophages, foam cells, and PMNs. Induction of the NLRP3 inflammasome enhances production and secretion of IL-1α, IL-1β with subsequent enhancement of inflammatory signals via IL-6 production. These processes entertain the smouldering embers of inflammation, consequently entailing the residual inflammatory risk (RIR) that negatively affects patient outcome. The right panel focuses on 'The Ugly', flaming burst of excess inflammation in the early phase after AMI. PMN activation and monocytes recruitment occur upon plaque rupture and thrombosis that is further increased by NET formation. The ensuing oxidative burst contributes to damage amplification during this early phase. Cytokines which are also present in 'The Bad', namely IL-1 and IL-6, show a particularly excessive surge in the early phase after AMI, their damaging characteristics thus potentiated during this phase. AMI, acute myocardial infarction; CRP, C-reactive protein; IL, interleukin; MACE, major adverse cardiovascular events; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NLRP, NOD-, LRR-, and pyrin domain-containing protein; NET, neutrophil extracellular trap; NK, natural killer cell; PAI1, plasminogen activator inhibitor 1; PMN, polymorphonuclear neutrophil; SAA, serum amyloid A; TIMPS, tissue inhibitors of metalloproteinases; TNF, tumour necrosis factor; Treg, regulatory T-cell.

Keywords Inflammation • Acute myocardial infarction • Anti-inflammatory therapy • Outcome

A new frontier—from lipids to inflammation

In the rogues gallery of medical conditions, cardiovascular diseases (CVD) still occupy the top spot on the 'Most Wanted' list of leading causes of morbidity and mortality worldwide.[1] Among CVD, acute myocardial infarction [AMI; ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI)] stand upon the prime offenders.[2] The management of AMI has advanced considerably, with early percutaneous coronary intervention (PCI) comprising the central pillar of treatment for patients with AMI.[2]

However, the consequences of coronary arterial flow interruption reach beyond the macroscopic scale of culprit lesions in the epicardial coronary arteries. In response to myocardial ischaemia, many crucial events occur at the cellular and molecular level in the myocardium. These sequelae include the death of cardiomyocytes, followed by successive waves of inflammatory cells an mediators.[3,4] Although to a degree necessary for myocardial healing, such processes, if left unchecked and allowed to proceed to an excessive degree, may lead to secondary damage, causing chronically impaired regional contractile function and adverse myocardial remodelling.

Contemporary guideline-based optimal medical therapy (OMT) directed at preventing recurrent thrombosis and atherosclerosis progression after AMI rests on several pillars, namely antithrombotic and antiplatelet agents, lipid-lowering therapy, drugs targeting the renin–angiotensin–aldosterone pathway, and beta-blockers.[2,5] Of note, these central building blocks of medical therapy to AMI patients do not as of yet feature any drugs targeted at post-AMI inflammation.

The value of later generation antiplatelet agents in secondary prevention for patients suffering AMI is well established.[6,7] Lipid-lowering therapies also have proven benefits for patients with AMI. Statins form the foundation,[8] followed by the addition of ezetimibe.[9] Recent trials have proven the clinical efficacy of antibody-based inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) in lowering recurrent cardiovascular events[10] and decreasing plaque progression.[11] The availability of bempedoic acid, of the long-acting RNA therapeutic inclisiran and the prospect of an oral PCSK9 inhibitor extend the potential of profound low-density lipoprotein cholesterol (LDL-C) lowering following AMI.[12–14]

Going beyond current OMT, recent evidence from experimental and clinical studies highlights the importance of cellular and molecular pathways related to inflammation and immunity in the setting of ischaemic myocardial injury. Increased inflammation precedes many cases of AMI, and in turn, excess inflammation invariably follows the acute event.[15]

Hence, despite the established importance of LDL-C as a causal risk factor for AMI, the story does not end at the 'cholesterol risk'. Half of asymptomatic patients with early subclinical atherosclerosis lack traditional cardiovascular risk factors such as smoking, hypertension, and dyslipidaemia.[16] Inflammation in both its chronic and acute forms may be one of these yet underappreciated risk factors: indeed, many patients presenting with AMI do not exhibit elevated LDL-C levels but show features of increased inflammation. Patients who have sustained AMI more commonly have residual inflammation, rather than residual elevated LDL-C.[17] Moreover, among patients receiving more intensive contemporary lipid-lowering therapy, inflammation assessed by high-sensitivity C-reactive protein (hsCRP) became a stronger predictor of future cardiovascular events than cholesterol assessed by LDL-C.[18] These findings support the notion that, as lipid risk is more stringently treated, the relative risk attributable to inflammation increases.[19]

This review highlights the deleterious and beneficial roles of different inflammatory cells and mediators during the early phase of heightened inflammatory activity, as well as the following low-grade residue of inflammation after AMI. It summarizes the current studies investigating anti-inflammatory therapy after AMI, targeting different time windows and pro-inflammatory mediators. Thereby, this review provides arguments for selecting the best suited patients, the ideal target pathways, and the optimal treatment regimen to administer anti-inflammatory treatment to patients with AMI. Harnessing this knowledge promises to yield substantial advances in the management of AMI patients.

Inflammation in acute myocardial infarction: the good, the bad and the ugly

The good—protection and repair

Organisms respond to various kinds of injury through inflammation.[20] Ischaemic cellular injury following AMI furnishes a familiar example. The resulting myocardial necrosis unleashes a cascade of inflammatory processes which, although in many ways potentially harmful, also scavenge debris and promote healing (*Graphical Abstract, left panel*).[3,4] Thus, controlled inflammation in this context is, at least in part, a vital repair process.

After AMI, successive waves of inflammatory cells and mediators can be distinguished in the damaged myocardium.[3,4] The first such wave of inflammation is dominated by polymorphonuclear neutrophils (PMNs) entering the myocardium. This seems to be the most damaging phase of post-AMI inflammation and will be discussed below.

During a second phase, primarily characterized by macrophage recruitment and following the initial infiltration of neutrophils, post-AMI inflammation exhibits some protective facets. The phagocytic macrophages remove debris and dead cells, and promote healing in the ischaemically damaged myocardium. Experimental findings support these beneficial effects, as depletion of macrophages after myocardial infarction augments mortality in mice.[21]

Alongside macrophages, T-cells are activated early after AMI in heart-draining mediastinal lymph nodes, presumably in part by autoantigens generated by the release of intracellular proteins upon myocardial damage.[22] Activation of regulatory T-cells (Tregs) can drive conversion of M1 (pro-inflammatory) slanted macrophages towards alternative M2 (anti-inflammatory) macrophages (*Table 1*, *Graphical Abstract*). By muting the maladaptive aspects of the post-AMI immune response, Tregs can promote healing after experimental AMI.[34]

Myocardial wound repair involves pivotal cytokines, namely interleukin (IL)-10 and IL-2, which orchestrate the crosstalk among T-cells and macrophages, eventually promoting tissue healing.[49] Type 2 helper T-cell (Th2)-derived cytokines, such as IL-4 and IL-13, also favour the acquisition of alternative M2 macrophage properties by M1-polarized macrophages.[34,50] Once activated by both Th2 cells and Tregs, M2 macrophages produce an array of mediators (e.g. insulin-like growth factor-1, fibronectin, transforming growth factor-β, IL-10, and vascular endothelial growth factor) thereby participating in myocardial healing.[51] Tregs exert similar protective roles in experimental atherosclerosis.[33] Interestingly, myocardial infarction induced pro-healing T-cell autoimmunity in both mice and humans.[35]

Table 1 Pro- and anti-inflammatory cells and mediators in atherosclerosis and myocardial infarction—experimental data and clinical evidence

EXPERIMENTAL		
Biomarker	**Atherosclerosis**	**AMI**
IL-1β	Anti-IL-1β-L: ↓ late athero[23] LOF IL-1β: ↓ athero[24]	
IL-1α	Anti-IL-1α: ↓ early athero[23] LOF IL-1α: ↓ athero[25]	IL-1α: early danger signal[26] Anti-IL-1α: ↓ inflammasome, ↓ infarct size[27] (I/R)
IL-6/IL-6	LOF IL-6: ↑ athero[28] rIL-6: ↑ athero[29]	LOF IL-6—**neutral** on AMI size/survival[30] (LAD ligation)
IL-2		ILC2: ↑ recovery after AMI[31] (LAD ligation)
IL-10	GOF IL-10: ↓ athero[32]	
Treg	Treg: ↓ athero[33]	↑ myocardial healing post-AMI[34,35] (LAD ligation)
CLINICAL		
Biomarker	**Atherosclerosis**	**AMI (with PCI, I/R)**
PMN	PMN: ↑ late lesions and atherothrombosis[36]	N/L: ↑ MACE[37,38] NETs released by culprit lesion predict infarct size[39]
IL-1β	Anti-IL-1β–L: ↓ MACE[40]	Anti-IL-1-R1: ↓ CRP[41] Ani-IL-1-R1: ↓ CRP[42]
IL-1α		IL-1α on monocytes of AMI and CKD: ↑ MACE[43]
IL-6	Anti-IL-6 L: ↓ infl & thromb[44]	Anti-IL-6-R: ↓ CRP,[45] ↑ myocardial salvage[46] ↑ IL-6: ↑ MACE[47]
IL-2		Low-dose IL-2 → ↑ ILC2[31]
Treg		AMI: ↓ Tregs[48]

ACS, acute coronary syndrome; AMI, acute myocardial infarction; athero, atherosclerosis; CKD, chronic kidney disease; CRP, C-reactive protein; GOF, gain of function; IL, interleukin; ILC2, innate lymphoid cell type 2; I/R, ischaemia–reperfusion; LAD, permanent left anterior descending coronary artery; LOF, loss of function; MACE, major adverse cardiovascular events; NET, neutrophil extracellular trap; N/L, neutrophil to lymphocyte ratio; PCI, percutaneous coronary intervention; PMN, polymorphonuclear leukocyte; rIL-6, recombinant interleukin-6; Treg, regulatory T-cell; damaging, protective.

$CD8^+$ cells also accumulate in the myocardium after myocardial infarction. At the experimental level, they play a *dual* role in the regulation of local inflammatory processes: while survival was improved after permanent coronary artery ligation in mice deficient in functional $CD8^+$ T-cells, left ventricular rupture rates were increased due to poor scar formation,[52] thus indicating a partially protective role of $CD8^+$ T-cells after AMI. However, at the clinical level, patients with AMI who presented with high numbers of $CD8^+CD28^+$ T-cells showed increased infarct size and worsened ventricular function.[53] Similarly, elevated levels of Granzyme B released from cytotoxic $CD8^+$ T-cells in patients with AMI predicted increased 1-year mortality.[54]

Finally, recent evidence also suggests a role for natural killer (NK) cells, a heterogeneous group of innate lymphoid cells, in the myocardial inflammatory response after AMI.[55] Although they may interact with M1 macrophages and promote inflammation, NK cells appear to have a predominantly protective[56] role as they are involved in IL-10 and IL-2-mediated immune cell crosstalk. After AMI, expansion of bone marrow-derived NK cells protects the heart by reducing cardiomyocyte apoptosis, collagen deposition, and promoting neovascularization.[57]

Such findings, identifying IL-10, IL-2, Th2 cells, and Tregs, along with further candidates, as potentially beneficial players in the inflammatory landscape after AMI, stimulated efforts to translate preclinical data into the clinical context. Lymphopenia after primary PCI in patients with AMI was associated with a poor prognosis.[48] Notably, a decrease of CD4 and $CD8^+$ T-cells was observed in the first 90 min after myocardial reperfusion and these T-cells were mostly recruited into the reperfused myocardium.

Furthermore, IL-2 at low concentrations increased levels of Tregs in atherosclerotic mice.[58] A protective and regenerative role of innate lymphoid cells type 2 (ILC2) has been suggested after experimental myocardial infarction.[31] Analyses of samples taken from the LILACS trial (low-dose interleukin 2 in patients with stable ischaemic heart disease and acute coronary syndrome)[49] have shown that administration of low-dose IL-2 promoted ILC2 expansion and activation in patients with ACS.[31] However, a potential therapeutic role of IL-2 awaits confirmation in larger ongoing trials.

These insights into the cardioprotective and restorative functions of inflammation after AMI beg the question as to potentially harmful consequences of untargeted anti-inflammatory therapy after AMI. Past observations support such concerns: glucocorticoids are potent, broad-spectrum anti-inflammatory agents. While they might partially attenuate deleterious features of inflammation, they may also impair its protective aspects.[59] In the infarcted heart, this effect could favour complications such as ventricular rupture,[60] raising safety concerns

about high-dose glucocorticoid therapy in patients with AMI.[61] The same concerns apply to non-steroidal anti-inflammatory drugs (NSAIDs). Several experimental studies have found that these agents can produce adverse effects on infarct healing and cardiac function.[59] Exposure to NSAIDs confers an increased risk for unwanted atherothrombotic and cardiorenal effects in patients with known coronary artery disease (CAD).[62]

Broadening our scope from the heart to the whole organism, inflammation plays a vital role during infection by fighting and eliminating infectious agents. Thus, targeting inflammation in any clinical setting, including AMI, may facilitate infections by interfering with host defence mechanisms.

If inflammation thus seems to be important in cardiac repair and host defence, why should we aim to target it when treating patients with AMI? The key underlying rationale was proposed long before our time. As the Swiss physician, alchemist, and philosopher Philippus Theophrastus Aureolus Bombastus von Hohenheim, more famously known as Paracelsus, proclaimed 500 years ago:

'Poison is in everything, and no thing is without poison. Solely the dose determines that a thing is not a poison.'—Third Defence, Paracelsus.

The bad—chronic low-grade inflammation

Paracelsus' logic dictates that although a certain degree of inflammation may be beneficial and even necessary for repair of ischaemic cardiac tissue, too much may prove deleterious. The smouldering, low-grade excess of inflammation persisting after AMI accounts for what has been coined the *residual inflammatory risk* (RIR). Residual inflammatory risk may affect patient outcome in several ways: long-term outcomes for patients suffering AMI depend on both local inflammatory processes inflicting damage upon the myocardial tissue, as well as inflammatory activity affecting atherosclerotic plaque progression. The latter aspect gains relevance when considering rates of recurrent AMI.

In this context, mounting evidence supports the role of PMNs in advanced atherosclerotic lesions and subsequent complications (*Table 1*; *Graphical Abstract, mid panel*).[36] Systemic inflammation involving activated PMNs associates with features of plaque instability; furthermore, increased PMNs in peripheral blood as well as increased neutrophil to lymphocyte ratio can predict adverse cardiovascular outcomes.[37,38] The detrimental effects of PMNs in atherosclerosis and plaque instability result mainly from increased monocyte recruitment and neutrophil extracellular trap (NET) formation.[63] Neutrophil extracellular traps have been localized at the site of human coronary culprit lesions.[39] The release of granular and cytoplasmatic proteins such as LL37 and S100A8/A9 mediate classical monocyte recruitment by PMNs.[36] Once formed, NETs aggravate local inflammation and plaque erosion by promoting macrophage accumulation, IL-1α activation, and type I interferon (IFN-1) release from plasmacytoid dendritic cells, promoting a pro-coagulant state.[64]

Subsequent induction of the NOD-, LRR-, and pyrin domain-containing protein (NLRP) 3 inflammasome, a macromolecular protein complex which activates caspase 1, leads to activation of pro-IL-1β, pro-IL-18, followed by amplification of inflammatory signals in the vasculature.[65] The main effects of IL-1β on vascular cells include: (i) increased tissue factor, leukocyte adhesion and pyrogenic prostaglandin production in endothelial cells; (ii) proliferation of vascular smooth muscle cells; (iii) release of several matrix metalloproteinases (MMPs) involved in collagen degradation and plaque instability; (iv) production of acute phase reactants [e.g. CRP, fibrinogen, plasminogen activator inhibitor (PAI)-1] and; (v) induction of inflammatory and metabolic signals in leukocytes favouring monocyte infiltration and plaque progression.[66] Interleukin-1β amplifies inflammation via two mechanisms: (i) induction of its own expression in different cell types; and (ii) increased production of IL-6.[67] Interleukin-6 reflects systemic and vascular inflammation and triggers the acute phase response. Interleukin-6 associates with leukocyte recruitment, as well as changes in adaptive immunity, promoting Th1/Th2 imbalance, macrophage polarization, or plaque destabilization.[68]

Translating such knowledge into clinical research, the recent RESCUE trial showed that the use of ziltivekimab—a fully human monoclonal antibody blocking the IL-6 ligand—reduced biomarkers of inflammation and thrombosis in patients with chronic kidney disease (CKD) and increased hsCRP.[44] On the grounds of these encouraging safety and efficacy data, the ongoing large-scale cardiovascular outcomes trial (ZEUS, NCT05021835) investigates the effects of ziltivekimab in patients with CKD, increased hsCRP, and established CVD.[69]

Two large-scale outcome studies confirmed the benefits of anti-inflammatory therapies targeting RIR in patients in the chronic phase after AMI: the first, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) studied >10 000 patients more than 30 days after AMI. CANTOS showed that antibody-mediated blockade of IL-1β in patients with history of AMI reduced recurrent cardiovascular events.[40] The second, the Colchicine Cardiovascular Outcomes Trial (COLCOT), enrolled >4700 patients within 30 days of the qualifying AMI. The Colchicine Cardiovascular Outcomes Trial showed that patients with recent AMI treated with low-dose colchicine had a lower risk of recurrent ischaemic cardiovascular events than the placebo group.[70] Complementary to COLCOT, the smaller Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease (LoDoCo2) trial showed that low-dose colchicine improved outcome in patients with chronic coronary syndromes (CCS).[71]

CANTOS selected patients at high-risk post-AMI due to RIR, as defined by hsCRP levels >2 mg/L. Patients in CANTOS had well-controlled LDL-C concentrations due to high-intensity statin therapy (median of 2.1 mmol/L on treatment). This is consistent with the notion that the RIR exists independently of residual risk. Of note, the most recent guidelines recommend even more aggressive lipid-lowering therapy in high-risk secondary prevention, achieving an LDL-C value of <1.4 mmol/L. As the residual lipid risk decreases thanks to continuous advances in lipid-lowering therapies and even more stringent guidelines, while the same do not yet consider any anti-inflammatory therapy other than colchicine,[72] the RIR gains relative importance.[19] Thus, in the broad landscape of secondary risk prevention after AMI, residual risk in patients well treated with statins may benefit from therapies that act by mechanisms orthogonal to LDL lowering, among them anti-inflammatory interventions.

Notwithstanding, CANTOS also indicated potential hazards of anti-inflammatory interventions. Patients treated with the IL-1β antibody canakinumab had a slightly, yet significantly higher incidence of fatal infections than patients receiving placebo. Similar observations were made in COLCOT. The challenges and opportunities now lie in finding the sweet spot in dosing regimens and novel targets, which straddle the border between quenching inflammation sufficiently to improve net clinical benefit without unduly compromising host defence.

By including patients in the chronic phase of inflammation post-AMI (≥30 and ≤30 days respectively), CANTOS[40] and COLCOT[70] have taught us the benefit of targeting the glowing embers of excessive low-grade inflammation constituting the RIR.[73] Hence, the RIR does in fact deserve the title of 'The Bad' and therefore should be considered in an optimal treatment regimen targeting post-AMI inflammation. However, where there is a smouldering ember, a flaming fire usually precedes.

The ugly—early burst of excessive inflammation

The study and characterization, and indeed the interest in treating inflammation in patients suffering AMI is now expanding from its chronic aspects to the acute setting, the flaming burst of excess inflammation after AMI.

The very early inflammatory response begins within the culprit lesion with PMN activation and monocyte recruitment upon plaque rupture and coronary occlusion, with local release of pro-inflammatory mediators such as IL-6.[74] These processes are amplified immediately after coronary recanalization, contributing to reperfusion injury.[75] The acute surge in cytokines boosts neutrophil activation, release of granule enzymes, such as myeloperoxidase and catalase, and the subsequent oxidative burst.[75] Processes which also contribute to 'The Bad', namely key cytokines (e.g. IL-1 and IL-6), NLRP3 activation and PMN-induced NET formation, show particularly excessive activity, accentuating their damaging characteristics during this phase (*Graphical Abstract, right panel*).

This very early, local phase of inflammation precedes an early systemic response, entailing a rise in systemic markers of inflammation. The measurements of such early pro-inflammatory markers, of which CRP is a prominent example and IL-6 has engendered growing interest, can stratify risk in patients post-AMI.

C-reactive protein peaks approximately 2–3 days after the onset of symptoms and its increase associates with an impaired short- and long-term prognosis.[76–79] Moreover, the peak of CRP correlates with post-AMI complications including ventricular remodelling, reduced ejection fraction, increased risk of heart failure, cardiac rupture, and death.[77,78] Many other inflammatory markers, namely the complement pathway and cleavage of C5, secretory phospholipase A2 (sPLA2), and lipoprotein-associated phospholipase A2 (Lp-PLA2) correlate with cardiovascular outcomes in patients post-AMI.[80]

Numerous smaller-scale trials have sought to treat this early burst of excessive inflammation. Targeting different pro-inflammatory pathways and implementing various treatment regimens, those trials have met with varied degrees of success (*Table 2*). Most promising results have come from trials targeting pathways related to the IL-1 family of cytokines. After two pilot trials, Virginia Commonwealth University Anakinra Remodeling Trial 1 (VCU-ART) and VCU-ART 2, the recently published VCU-ART 3 trial[41] enrolled a total of 99 patients presenting early (<12 h) after STEMI. Anakinra, an IL-1 receptor antagonist that blocks the action of both IL-1α and β, was administered once within the first 12 h after AMI and subsequently every 24 h for a total of 14 days. C-reactive protein surged in the placebo group as expected. Administration of the anti-inflammatory drug reduced hsCRP levels in the treatment group, particularly during the initial burst of inflammation. This attenuation of early inflammation post-AMI was associated with fewer clinical events related to heart failure, although this small study lacked power for standard rates of major adverse cardiovascular events (MACE).

Moving a step further downstream in the IL-1-related pathways, the pro-inflammatory cytokine IL-6 has gained attention in the acute setting of post-AMI inflammation. The recent ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction (ASSAIL-MI) Phase 2 trial investigated the effects of very early IL-6 receptor blockade with tocilizumab in STEMI patients presenting 6 h after symptom onset.[46] Myocardial salvage was modestly increased without affecting infarct size in cardiac magnetic resonance (CMR) at 3–7 days in the treatment group. Additionally, systemic levels of hsCRP were lower in the treatment group. Interestingly, the effect on myocardial salvage was only seen in the subgroup of patients presenting within 3–6 h after symptom onset. No effect was seen in those patients presenting within ≤ 3 h.

Despite the promising findings of these studies, attempts to target 'The Ugly', early inflammatory response during AMI have not shown any breakthrough clinical success so far. Thus, the task remains to identify an effective and safe agent, the optimal dose, timing, and duration of administration of an anti-inflammatory agent post-AMI.

Most wanted: 'the ugly' and 'the bad'—how can they be captured?

Table 2 depicts a selection of trials targeting post-AMI inflammation and showing their design as well as their respective outcomes.[40–42,45,46,70,81–92] A thorough analysis of the different treatment regimens applied as well as their correlation to respective outcomes suggests the following conclusions and implications for designing future studies:

Start therapy early—but not too early

Quelling the initial surge of excess inflammation post-AMI, optimal anti-inflammatory treatment to patients with AMI requires the targeting of early inflammatory mediators and administration of anti-inflammatory therapy in the very early stages (e.g. ≤ 12 h) after the initial ischaemic insult. A treatment regimen targeting the early phases of the excessive and deleterious aspects of post-AMI inflammation may limit subsequent myocardial damage.

This conjecture derives support from the above-mentioned VCU-ART and ASSAIL-MI trials. Both trials targeted the early (≤12 and ≤ 6 h after symptom onset, respectively) phase of post-AMI inflammation with promising results.

In contrast, the recently published Controlled Level EVERolimus in Acute Coronary Syndromes (CLEVER-ACS) trial enrolled patients within a time window of up to 5 days after PCI.[93] The trial showed negative results regarding its primary CMR-based endpoint. Firstly, the chosen target (murine target of rapamycin) is broad and relatively unspecific as to targeting 'The Bad'. The following section on the selection of precise, downstream targets will further elucidate this point. Secondly, the chosen time window of treatment initiation within up to 5 days post-PCI may be too late to adequately capture 'The Ugly'.

Although supporting the proposed concept, the ASSAIL-MI also highlights a potential caveat: In the subgroup of patients presenting ≤ 3 h after symptom onset, no treatment effect was observed. In this particular group of patients, the ischaemic myocardium may have been reperfused too quickly for any substantial myocardial injury and subsequent spike in inflammation to have taken place. Thus, in very early presentations, the overwhelming benefit of revascularization by PCI might limit the effects of subsequent anti-inflammatory therapy.

It is important to note that this latter point does not contradict the previous statement that early anti-inflammatory therapy is desirable. Future studies should target a time window tailored to recruit patients with substantial burden of post-AMI inflammation while still hitting early enough as to not miss the crucial surge in excessive damaging inflammation.

Follow-through treatment

Two earlier trials have studied the effects of pexelizumab (antibody targeting complement factor 5), the Complement Inhibition in Myocardial Infarction Treated with Angioplasty (COMMA)[90] and Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI)[88] trials.

Table 2 Trials studying the effects of anti-inflammatory therapy for myocardial infarction

Trial	IMP	Study population	Phase of MI	Study design	*N*	IMP delivery protocol	Duration of IMP delivery	Effect on clinical outcome	Effects on structural parameters	Effects on functional parameters	Effects on biomarkers
CANTOS	Canakinumab (anti-IL-1β −AB)	H/o MI ≥ 30 days prior to randomization, presence of RIR as defined by hsCRP ≥ 2 mg/L	Late	Phase 3 RCT	10 061	First dose > 30 days after MI, then every 3 months	Median f/u = 3.7 years	Lower rate of recurrent cardiovascular events			Reduction in CRP and IL-6 levels
VCU-ART	Anakinra (IL-1RA)	STEMI with <24 h since onset of chest pain with successful PCI	Acute (<24 h)	RCT, pilot	10	First dose within 24 h since onset of chest pain, after successful PCI, then every 24h	14 days		No difference in infarct size measured by CMR	Reduction in LVESVi	
VCU-ART2	Anakinra	STEMI with <24 h since onset of chest pain with successful PCI	Acute (<24 h)	RCT, pilot	30	First dose within 24 h since onset of chest pain, after successful PCI, then every 24 h	14 days			No significant difference in LVESVi, LVEDVi, and LVEF	Blunted interval change in CRP between admission and 72 h
VCU-ART3	Anakinra	STEMI with PCI within 12 h after onset of symptoms	Acute (<12 h)	Phase 2 RCT	99	First dose within 12 h of PCI, then every 24 h	14 days	Lower incidence of HF-related clinical events		No difference in LVESV or LVEF	Decrease in AUC of hsCRP during the first 14 days post-STEMI
MRC-ILA	Anakinra	NSTEMI presenting within 48 h of symptom onset, no intention of urgent revascularization within 3 months	Subacute (<48 h)	Phase 2 RCT	182	First dose within 24 h of positive Trop, then every 24 h	14 days	Significant increase in MACE at 1-year f/u	No difference in CMR sub-study		Decrease in AUC of hsCRP during the first 7 days of treatment, increase in absolute hsCRP from Day 14 to Day 30, decrease in white cell count over treatment period, no difference in AUC of Trop during the first 7 days

Continued

Table 2 *Continued*

Trial	IMP	Study population	Phase of MI	Study design	*N*	IMP delivery protocol	Duration of IMP delivery	Effect on clinical outcome	Effects on structural parameters	Effects on functional parameters	Effects on biomarkers
COLCOT	Colchicine	MI within 30 days prior to enrolment that have undergone PCI and were on OMT	Late	Phase 3 RCT	4745	First dose within 30 days after MI, after completion of PCI, then daily doses	Ca. 23 months	Lower incidence of ischaemic cardiovascular events			Trend towards lower CRP
CLEVER-ACS	Everolimus	STEMI within 5 days of PCI	Subacute	Phase 2 RCT	150	Daily oral dose for 5 days	5 days		No difference in infarct size or microvascular obstruction (CMR)		
CIRT	Methotrexate	H/o MI and/or multivessel CAD with completion of planned revascularization plus either T2-DM or metabolic syndrome, medically stable for ≥60 days from index MI	Late	Phase 3 RCT	4786	Weekly dose of MTX plus folate daily	Median f/u = 2.3 years	No difference in cardiovascular events and all-cause mortality			No reduction in CRP levels, IL-1β, or IL-6
Trial	IMP	Study population	Phase of MI	Study design	N	IMP delivery protocol	Duration of IMP delivery	Effect on clinical outcome	Effects on structural parameters	Effects on functional parameters	[a]Effects on biomarkers
Piot *et al.*	Cyclosporine	STEMI presenting within 12 h after onset of symptoms	Acute (<12 h)	RCT, pilot	58	Single bolus dose immediately before PCI			Reduction of infarct size in CMR 5 days post-PCI	No difference in LVEF after 3 months	Reduction in AUC for CK within first 72 h, non-significant reduction in AUC for Trop-I
CIRCUS	Cyclosporine	STEMI presenting within 12 h after onset of symptoms with culprit lesion in LAD	Acute (< 12 h)	Phase 3 RCT	970	Single bolus dose immediately before PCI		No reduction in death from any cause, worsening of HF during the initial hospitalization, rehospitalization for heart failure		No difference in LVEF, LVEDV, or LVESV	No difference in total CK at any timepoint

Continued

Table 2 *Continued*

Trial	IMP	Study population	Phase of MI	Study design	*N*	IMP delivery protocol	Duration of IMP delivery	Effect on clinical outcome	Effects on structural parameters	Effects on functional parameters	Effects on biomarkers
CYCLE	Cyclosporine	STEMI presenting within 6 h after onset of symptoms	Acute (<6 h)	Open-label, Phase 2 RCT	410	Single bolus dose immediately before PCI		No difference in combined endpoint of all-cause mortality, cardiogenic shock and HF		No difference in LVEF	No difference in Trop-T or CK
Kleveland *et al.*	Tocilizumab (anti-IL-6-AB)	NSTEMI scheduled for coronary angiography, median of 2 days after onset of symptoms	Subacute (mean of 2 days)	Phase 2 RCT	117	Single bolus dose immediately before coronary angiography				No difference in LVEF	Reduction in AUC for hsCRP and Trop-T within 3 days
ASSAIL-MI	Tocilizumab	STEMI presenting within 6 h after onset of symptoms	Acute (<6 h)	Phase 2 RCT	299	Single bolus dose during PCI			Increased myocardial salvage and lower microvascular obstruction at 3–7d		Reduction in AUC for hsCRP during hospitalization
APEX-AMI	Pexelizumab (anti-C5-AB)	STEMI presenting within 6 h after onset of symptoms scheduled for PCI	Acute (<6 h)	Phase 3 RCT	5745	Single bolus dose prior to PCI		No difference in 30-day-mortality, HF, shock, or recurrent MI			
Sub-study of APEX-AMI	Pexelizumab	Idem	Idem	Sub-study	99	Idem			Reduced infarct size at baseline (Day 5) and f/u (Day 90) in CMR	Improved LVEF by CMR	
COMMA	Pexelizumab	STEMI presenting within 6 h after onset of symptoms scheduled for PCI	Acute (<6 h)	Phase 3 RCT	960	Bolus dose prior to PCI followed by infusion with start 4 h after first dose	20 h	Reduction in mortality at 90 days			No difference in AUC for CK

AB, antibody; AUC, area under the curve; C5, complement component 5; CAD, coronary artery disease; CK, creatinine kinase; CMR, cardiac magnetic resonance; CRP, C-reactive protein; f/u, follow-up; hs, high-sensitivity; H/o, history of; IL-1RA; interleukin-1 receptor antagonist; MI, myocardial infarction; LAD, left anterior descending coronary artery; LVESVI, left ventricular end-systolic volume index; LVEDVI, left ventricular end-diastolic volume index; LVESV, left ventricular end-systolic volume; MTX, methotrexate; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; Trop, troponin; for abbreviations of trials, please refer to the text.

Both included STEMI patients within 6 h after onset of symptoms (APEX-AMI: 5745 patients, COMMA: 960 patients). Of note, as both studies recruited patients between 2000 and 2006, the background therapy used in that era does not reflect contemporary AMI management. Notably, the residual lipid risk at that time was still of considerable relevance and thus, the proportional RIR was lower. Moreover, the Guidelines for CVD prevention at that time comprised different aims regarding cardiovascular risk factor control including less stringent lipid-lowering therapy. These factors should be considered when interpreting their results.

The COMMA trial showed superiority of a bolus of pexelizumab (antibody targeting complement factor 5) followed by an infusion of the drug as opposed to bolus-only treatment or placebo regarding 90-day-mortality.[90] In APEX-AMI, patients only received a single dose of the complement inhibitor before PCI. This treatment did not translate into any significant difference in clinical outcomes. However, a CMR-based sub-study did find reduced infarct size and improved left ventricular ejection fraction in the treatment group.[89]

Quelling early post-AMI inflammation may target adverse effects of excess inflammation on myocardial healing. However, this still leaves the RIR unaddressed; to target RIR, a single early dose of anti-inflammatory therapy might not suffice. With myocardial damage being the first and early target of anti-inflammatory therapy after AMI, the resulting increased plaque progression may comprise another target of interest. In support of this notion, mice with experimental myocardial infarction showed subsequent activation of inflammatory cells that enhanced atherosclerotic lesions.[94] In the setting of secondary prevention after AMI, suppressing inflammation might thus not only benefit the myocardial tissue itself by limiting secondary damage but also play a role in preventing recurrent cardiovascular events by limiting inflammation-driven progression of atherosclerosis.

The Cyclosporine Improve Clinical Outcome in STEMI Patients (CIRCUS)[86] and CYCLosporinE A in Reperfused Acute Myocardial Infarction (CYCLE)[87] trials show also limited effects of a single early treatment. Both trials tested a single early bolus dose of cyclosporine before PCI (CIRCUS < 12 h; CYCLE < 6 h after symptom onset) and showed no difference in clinical outcomes. In contrast, the two large outcome trials COLCOT and LoDoCo2, both implementing longer-term therapy with colchicine, established the efficacy of follow-through treatment. Such data support testing a regimen which encompasses both the early and later phases of post-AMI inflammation to mitigate myocardial damage and later plaque progression, thus preventing re-ignition of the acute inflammatory flame with recurrent cardiovascular events.

Target patients with large inflammatory burden

Large myocardial infarctions with more ischaemically damaged tissue unleash larger amounts of inflammatory mediators, ensuing a higher degree of excessive acute inflammatory response. Patients with large myocardial infarction, and thus large inflammatory burden, may derive more benefit from early anti-inflammatory interventions. One readily attainable surrogate for infarct size may be furnished by the presence of ST-segment elevation, i.e. by the selection of patients presenting with STEMI rather than NSTEMI.

The relatively small VCU-ART trials (STEMI) and MRC-ILA[42] (NSTEMI) both administered the IL-1-receptor antagonist anakinra using a similar regimen; an initial early dose, followed by continued daily administration for 14 days, with the notable difference that patients in MRC-ILA were included in a later phase (48 h after onset of symptoms vs. <12 h for VCU-ART3). While both trials showed trends towards favourable outcomes in early follow-up, MRC-ILA showed an increase in MACE at 1 year in the treatment group. These differences in outcome could relate to enrolment of NSTEMI vs. STEMI. In MRC-ILA, patients with NSTEMI might have presented less inflammatory burden, thus furnishing a narrower therapeutic window and higher chance for adverse side effect for anti-inflammatory therapy than the STEMI patients included in VCU-ART3. Following the same rationale, the recent ASSAIL-MI trial was targeted at patients with STEMI.[45]

The challenge in selecting patients with large AMI lies within balancing timeliness and precision of estimation of infarct size. Although being the undisputed reference standard for measuring infarct size, CMR is not suitable for selecting patients for anti-inflammatory treatment in a timely fashion. As described, ECG features and the resulting selection of patients with STEMI may offer a rough surrogate for infarct size. The use of readily available biomarkers of inflammation (e.g. CRP or IL-6) and of myocardial injury (e.g. cardiac troponin) could further improve the selection of patients with AMI most likely to benefit from anti-inflammatory therapy. Further research is needed to enable timely identification of patients with large AMI and their optimal surrogate markers for anti-inflammatory therapy.

Choose the suitable pro-inflammatory target: hit the harmful, spare the protective

One of the key challenges of anti-inflammatory intervention in general, and more specifically in the context of AMI, lies in avoiding interference with host defence and healing. In this regard, the selection of downstream mediators in the inflammatory pathways as pharmaceutical targets may minimize unwanted effects. The potential adverse effects of treatments with corticosteroids and NSAIDS discussed above highlight the possible hazards of broad-spectrum agents in the context of AMI. Optimal anti-inflammatory therapy to patients with AMI should thus be targeted with precision at the harmful and excessive facets of post-AMI inflammation ('The Bad' and 'The Ugly'), while maintaining those functions related to myocardial repair and healing ('The Good'). Understanding in detail and with high temporal resolution which key cellular or molecular elements of post-AMI inflammation contribute to either 'The Good', 'The Bad' or 'The Ugly' will pave the way to achieve this goal.

As to the choice of the specific targets, preclinical evidence as well as several recent trials highlight the importance of IL-1-related pathways, including both isoforms IL-1α and IL-1β, as well as their downstream mediator IL-6. These targets appear particularly promising as they provide evidence in atherosclerosis as well as in AMI, at the experimental and clinical level (*Table 1*).

Interleukin-1α

The role of IL-1α remains largely unexplored in the setting of AMI. However, evidence points towards an important role of this target: In the experimental setting, IL-1α is a crucial early trigger of inflammation after myocardial infarction.[26] Inhibition of IL-1α reduces inflammasome activation, decreases infarct size, and preserves left ventricular function in a model of murine myocardial infarction.[27] At the clinical level, increased IL-1α levels on monocytes of patients with AMI and CKD were associated with increased MACE.[43] Clinical trials in patients with AMI are still to be performed, leaving interesting opportunities for future research.

Interleukin-1β

While the other isoform of IL-1, i.e. IL-1β, has been established as a valuable target in the later phase after AMI by the CANTOS trial as described above, its role and kinetics in the acute phase of post-AMI remain less clear. Future trials might wish to explore this aspect.

Interleukin-6

Another target of potential interest is IL-6, downstream of the aforementioned IL-1 isoforms and their receptor. The ASSAIL-MI trial discussed above showed promising effects of early IL-6 receptor blockade after STEMI.[46] RESCUE demonstrated benefits in a more chronic setting of inflammation, where patients at high atherosclerotic risk showed decreased markers of inflammation and thrombosis upon anti-IL-6 ligand treatment.[44] The ongoing ZEUS trial is testing this concept in patients with established CVD.[69] Taken together, these studies suggest benefits of targeting the IL-6 pathway both in the early as well as in the later phases of post-AMI inflammation. Of note, RESCUE and ZEUS both target the IL-6 ligand, while ASSAIL-MI targeted the IL-6 receptor. The rationale for receptor blockade may be more compelling in that more efficient inhibition of the pathway may be achieved. However, such an approach may confer safety concerns as complete pathway inhibition at the receptor level may critically limit signalling of other protective downstream pathways and thus, impair defence and repair mechanisms. The effects of blocking the IL-6 ligand in AMI remain to be addressed.

When comparing inflammatory targets in atherosclerosis and myocardial infarction in mice and humans (*Table 1*), it is noteworthy that not all experimental studies modulating pro-inflammatory cytokines show uniform findings: Both constitutive deletion of IL-6[28] and recombinant IL-6[29] increased atherosclerosis in mice. This may suggest that baseline levels of IL-6 are protective, whereas excessive levels are damaging. Moreover, most patients with AMI undergo PCI, thus presenting an ischaemia/reperfusion (I/R) scenario, whereas I/R models are rarely applied in experimental AMI models. Where such models are applied, they poorly reflect the clinical context (no coronary atherothrombosis, no PCI, variable ischaemia time windows, etc.).

This selection of potential targets presents but a few of all possible targets and does not claim completeness. Moreover, we have previously discussed the potentially beneficial role of certain inflammatory mediators in the setting of AMI, such as IL-2 and IL-10. Therapeutic amplification of such pathways may provide an altogether different approach to inflammation-related therapy after AMI, worthy of further investigation.

Model of deleterious post-AMI inflammation

These considerations inform a proposed model of deleterious post-AMI inflammation as well as an approach to optimally target inflammation post-AMI (*Figure 1*). The degree of *baseline inflammation*

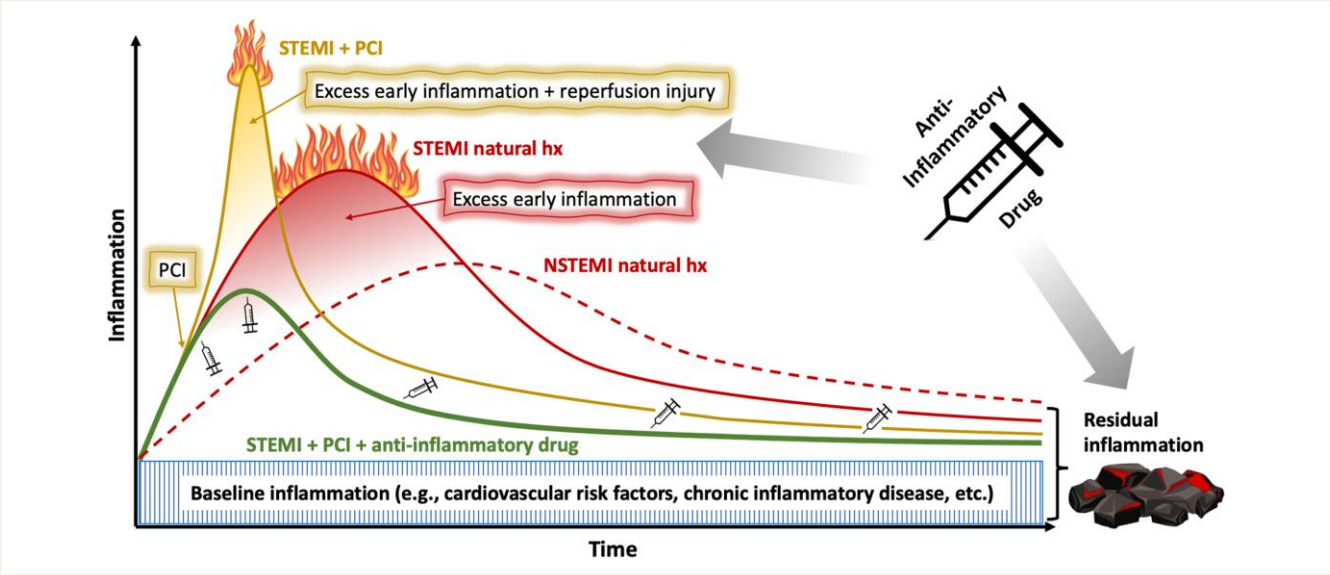


Figure 1 Putative model for the natural history of ST-segment elevation myocardial infarction vs. non-ST-segment elevation myocardial infarction and the potential effects of percutaneous coronary intervention and anti-inflammatory drugs. Baseline inflammation comprises a chronic level of activity of a patient's immuno-inflammatory system, determined by traditional cardiovascular risk factors as well as other comorbidities. On top of this chronic inflammation, ST-segment elevation myocardial infarction results in an acute excessive surge of inflammation, both of higher grade and earlier onset compared with non-ST-segment elevation myocardial infarction. Early percutaneous coronary intervention is the gold standard in the treatment of patients with ST-segment elevation myocardial infarction and its beneficial effects on outcome are undisputed. However, percutaneous coronary intervention elicits an additional spike in inflammation caused by local release of inflammatory mediators from balloon and stent expansion, distal microemboli as well as reperfusion injury. Though by far outweighed by the positive aspects of early percutaneous coronary intervention, these effects of reperfusion injury on post-ST-segment elevation myocardial infarction inflammation should not be neglected. Early anti-inflammatory therapy is anticipated to attenuate this early excessive inflammation after ST-segment elevation myocardial infarction. Extending treatment throughout the follow-up period suppresses the residual inflammatory risk (RIR), for which a causal role on patient outcome has been proven. AMI, acute myocardial infarction; hx, history; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

(*Figure 1*, area hatched in blue, 'Baseline inflammation') depends in part on the control of traditional cardiovascular risk factors such as dyslipidaemia and diabetes,[95] as well as other comorbidities, particularly chronic inflammatory diseases.[96]

STEMI (*Figure 1*, red line, 'STEMI natural hx') results in an *early excessive surge of deleterious inflammatory mediators*, on top of chronic baseline inflammation (acute-on-chronic). This burst of inflammation elicits a systemic rise of inflammatory markers including hsCRP. Left untreated, this early burst of excess inflammation can prove deleterious, rendering it 'The Ugly'.[94]

After this initial burst of damaging inflammation, despite guideline-directed secondary prevention measures, many patients still harbour *residual embers of low-grade inflammation*, the *RIR*. Targeting RIR in CANTOS proved the causal association of therapy directed against IL-1β with improved cardiovascular outcome for patients with CCS. Moreover, AMI patients with adequate control of cardiovascular risk factors, genuine low LDL-cholesterol and low triglyceride levels, may present a subgroup in which the RIR plays a particularly important role.

NSTEMI (*Figure 1*, red dashed line, 'NSTEMI natural hx') also elicits an inflammatory response. Like the VCU-ART trial demonstrated for patients with STEMI, the MRC-ILA study[42] reported an initial rise of hsCRP in patients with NSTEMI. However, in contrast to STEMI, the inflammation in NSTEMI rises more slowly and generally to a lesser extent.[79] This may result from the usually smaller infarct size in NSTEMI. The earlier and more intense inflammation in STEMI likely render it more suitable for testing an anti-inflammatory therapy than NSTEMI.

Beyond the inherent inflammatory response after AMI, treatment by primary PCI may add inflammatory load by local arterial and perivascular injury due to balloon and stent expansion as well as in response to distal microemboli and myocardial reperfusion (*Figure 1*, yellow line, 'STEMI + PCI').

Conclusions—target 'The Bad' and 'The Ugly', spare 'The Good'

Our understanding of the inflammatory processes that lead to and follow AMI have increased beyond the culprit plaque, to encompass the ensuing inflammatory response in the evolving infarction. The early burst of excessive inflammation during AMI as well as the subsequent RIR present promising targets for medical intervention beyond current standard care. With all three tightly interlinked, the challenge in treating post-AMI inflammation remains to attenuate the fire set aflame by 'The Ugly', contain the smouldering embers entertained by 'The Bad', thus preventing recurrent events and flare-ups of 'The Ugly', all while sparing the protective and healing nature of 'The Good'. An optimally tailored regimen for anti-inflammatory treatment post-AMI should fulfil the following criteria: *selection of the best suited patients, the ideal target, the optimal time window, and the best tailored dosing regimen, encompassing both acute as well as follow-through treatment.*

Such a treatment regimen might be designed along following key criteria:

- Select patients with large inflammatory burden.
- Choose a specific causal target.
- Treat early (capture 'The Ugly'), but not too early (e.g. > 3 h).
- Follow through with treatment (target 'The Bad') with a tapering regimen (spare 'The Good').

Extending our horizon, such an approach may not only be tested in patients with AMI, but also in other clinical scenarios of acute-on-chronic inflammation, such as stroke, acute limb ischaemia, or pulmonary embolism. Thus, the new frontier of anti-inflammatory therapy indeed looks promising and merits rigorous clinical evaluation in appropriately powered and designed outcome trials.

From present to future—the new frontier

Having gained valuable knowledge through past encounters with 'The Good', 'The Bad' and 'The Ugly', we still strive to better understand these aspects and to translate our insights to practice. Current guideline-based treatment for patients suffering AMI does not yet include anti-inflammatory therapy.

Our current scientific enterprise has identified many triggers, effector cells, and mediators in the inflammatory landscape implicated in AMI. Modern high throughput screening tools with pathway analyses, single nucleotide polymorphisms and genome-wide association studies, supported by artificial intelligence still await application in the highly dynamic setting of early post-AMI inflammation. Such tools may allow for characterization of the most relevant biomarkers, their respective kinetics, as well as identification of yet unknown relationships and causalities, ultimately resulting in selection of the most promising target and time window for therapeutic intervention. Rigorous clinical trials testing such early, targeted anti-inflammatory therapy in patients with AMI against hard clinical endpoints may pave the way to implementation into guideline-based, routine clinical practice.

Declarations

Disclosure of Interest

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Data Availability

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