Redefining residual inflammatory risk after acute coronary syndrome

Article *in* Future Cardiology · August 2021

DOI: 10.2217/fca-2021-0032

11 authors, including:

Marco Giuseppe Del Buono
Policlinico Universitario Agostino Gemelli
120 PUBLICATIONS **1,529** CITATIONS
SEE PROFILE

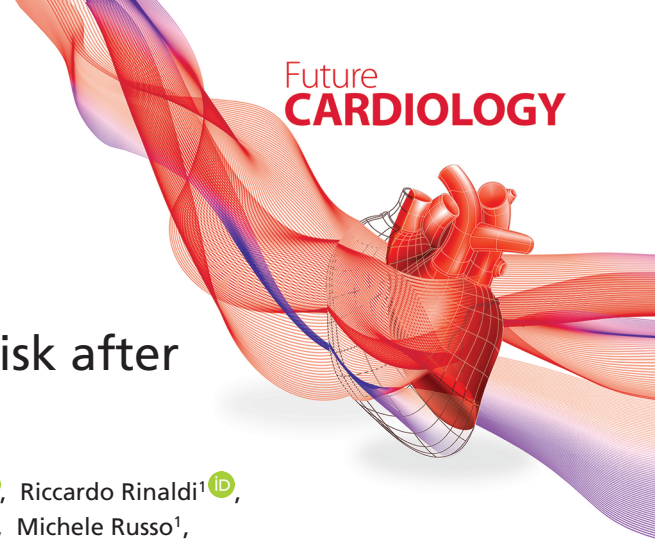
Rocco Antonio Montone
Policlinico Universitario Agostino Gemelli
155 PUBLICATIONS **1,836** CITATIONS
SEE PROFILE

Giulia Iannaccone
Policlinico Universitario Agostino Gemelli
31 PUBLICATIONS **205** CITATIONS
SEE PROFILE

Riccardo Rinaldi
Catholic University of the Sacred Heart
17 PUBLICATIONS **35** CITATIONS
SEE PROFILE

Special Report

Future CARDIOLOGY



Redefining residual inflammatory risk after acute coronary syndrome

Marco G Del Buono[1], Rocco A Montone*[,2], Giulia Iannaccone[1], Riccardo Rinaldi[1], Giulia La Vecchia[1], Massimiliano Camilli[1], Filippo L Gurgoglione[1], Michele Russo[1], Marco Lombardi[1], Domenico D'amario[1,2] & Giampaolo Niccoli[1,3]

[1]Department of Cardiovascular & Pulmonary Sciences, Catholic University of The Sacred Heart, Rome, Italy
[2]Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3]Cardiology Division, Parma University, Parma University Hospital, Via Gramsci, Parma, Italy
*Author for correspondence: Tel.: +39 06 3015 4187; rocco.montone@gmail.com

Over the last decades, inflammation proved to play a pivotal role in atherosclerotic plaque formation, progression and destabilization. Several studies showed that the patients presenting with acute coronary syndrome are at increased risk of adverse cardiovascular events at both short- and long-term follow-up. Results from different clinical trials highlighted that a residual inflammatory risk exist and targeting inflammation is a successful strategy in selected cases associated to an increased inflammatory burden. Recently, the optimization of intracoronary and multimodality imaging allowed to also assess the entity of local inflammation, thus encouraging the individuation of plaque characteristics that portend a higher risk of future cardiovascular events. In this short review, we aim to highlight the role of systemic and local inflammation in acute coronary syndromes, to provide a summarized overview of the possible medical strategies applicable in selected cases and to underline the diagnostic and prognostic potential of multimodality imaging.

First draft submitted: 17 February 2021; Accepted for publication: 4 June 2021; Published online: 16 August 2021

Keywords: acute coronary syndromes • percutaneous coronary interventions • personalized medicine

Inflammation plays a key role in atherosclerosis development and progression and in many patients the persistence of subclinical systemic inflammation may contribute to the recurrence of atherothrombotic events [1]. In this article, we discuss the newest evidences supporting the role of inflammation in the pathogenesis of atherosclerotic cardiovascular disease and the considerable residual inflammatory risk (RIR) that persists in patients after an acute coronary syndrome (ACS). We aim to address the importance of systemic and local parameters of ongoing subclinical vascular inflammation (e.g., evidence of high risk plaque features) highlighting the emerging role of invasive and multimodality imaging in predicting the recurrence of cardiovascular events and their potential application as a dynamic marker of therapeutic response to reduce the RIR.

Define 'residual inflammatory risk'

Despite large progresses in the acute treatment of ACS and the optimization of the secondary prevention measures, a considerable 'residual risk' persists as approximately 30% of patients experience a recurrent coronary episode within 3 years following an ACS (Figure 1) [2]. Most attempts to address residual risk have focused on platelet inhibition using more potent antiplatelet drugs or low-dose anticoagulation therapies, and on reducing low-density lipoprotein (LDL)-cholesterol using more potent LDL-lowering drugs [3–6]. Recent data from randomized clinical trials have consistently demonstrated that RIR, defined as high sensitive C-reactive protein (hs-CRP) $\geq$2 mg/dl and LDL-C <70 mg/dl, is not uncommon ranging from 29 to 37% according to the studies [5–7], a prevalence that rises up to 47% when LDL concentration is not considered [8]. In 1994, Liuzzo *et al.* showed for the first time the prognostic value of high CRP among patients with an ACS, demonstrating that those with CRP levels >0.3 mg/dl had a higher incidence of recurrent ischemia than those with CRP level <0.3 mg/dl [9]. Results from two sub-studies of the GUSTO IV ACS and the PROVE IT-TIMI 22 trials showed similar outcomes in patients with recent history

Future Medicine

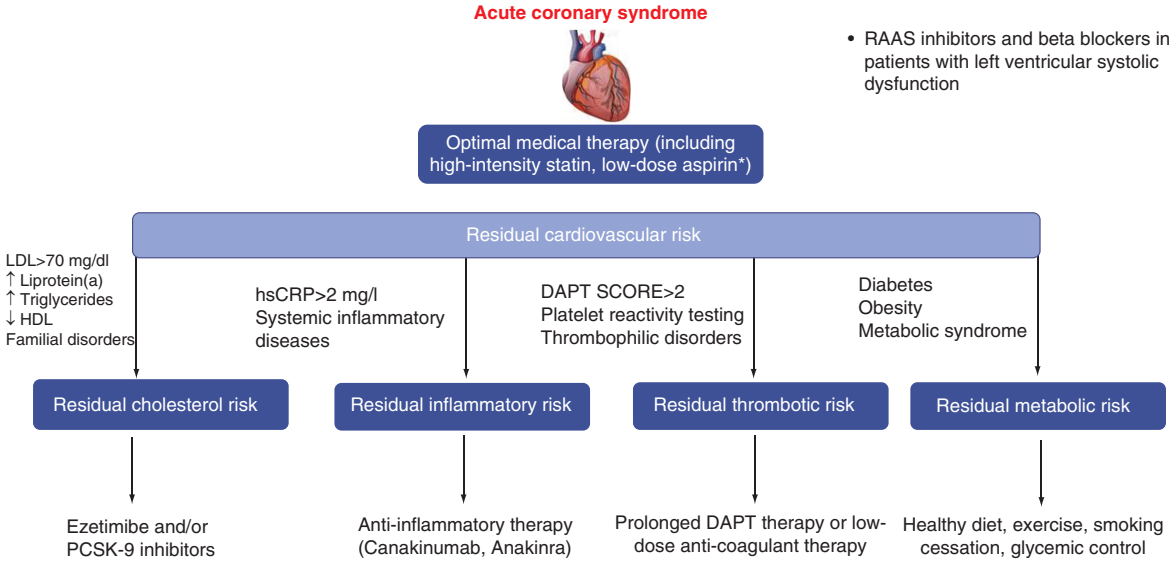


Figure 1. Strategies to address residual cardiovascular risk after acute coronary syndrome. Residual cardiovascular risk can be conferred by a plethora of different factors, including residual cholesterol risk (low HDL cholesterol, elevated levels of serum triglycerides, lipoprotein(a), LDL cholesterol and/or familiar hypercholesterolemia), residual metabolic risk (unhealthy diet, poor exercise, metabolic syndrome, diabetes mellitus), residual thrombotic risk and residual inflammatory risk and ongoing chronic inflammation.
DAPT: Dual antiplatelet therapy; hsCRP: High-sensitivity C-reactive protein.

of ACS and higher prevalence of ongoing chronic inflammation. The GUSTO IV ACS trial enrolled 7800 patients with an ACS without ST elevation who were not referred to coronary intervention, to investigate long-term effects of the glycoprotein IIb/IIIa inhibitor, abciximab. A sub-study was performed stratifying this population in quartiles according to hsCRP and Troponin-T levels with the aim to evaluate the correlation between these two biomarkers and short-term outcomes, defined as mortality rate at 30 days [10]. An elevated CRP level was defined as a CRP value ≥10 mg/l, centrally measured quantitative troponin T levels ranged from 0.01 to 17.3 μg/l, and quartile limits were 0.01, 0.12 and 0.47 μg/l. Mortality rate at 30 days ranged from 0.3 to 9.1% for patients in the lowest to the highest quartiles of both biomarkers, respectively, and CRP and troponin T were found to have an independent and complementary prognostic significance [10]. RIR is therefore associated with a clinically relevant elevation in the risk of MI, stroke and all-cause mortality [7,9].

Serum gamma-glutamyltransferase (GGT) activity, a widely used marker of liver function, has been recently emerged as an independent risk factor for cardiovascular or all-cause mortality in patients with CAD [11]. The fraction with highest molecular weights, (b-GGT) has been demonstrated to correlate with other histological markers of plaque vulnerability, as pro-inflammatory macrophages (M-1 like) [12], which may provide a source of b-GGT within the atheroma. Furthermore, GGT activity can promote pro-oxidant reactions and low-density lipoprotein (LDL) oxidation [13]. GGT has shown an independent predictor of cardiac mortality and nonfatal MI among patients with history of ischemic heart disease, thus suggesting its possible role as prognostic predictor of cardiovascular events recurrence and RIR assessment [14].

Interestingly, effectors of allergic inflammation also have been proven to play a role in coronary artery disease (CAD) progression and destabilization and to be related to the occurrence of adverse events following stent implantation [15].

The recognition of an RIR opened the way for exploring targeted anti-inflammatory therapies as a new tool in addition to current treatments for those patients at higher RIR. Inflammatory biomarkers (i.e., hs-CRP) are easy to measure, inexpensive, widely used to assess and quantify residual inflammatory risk and independently associated with cardiovascular events.

Strategies to target residual inflammatory risk

Recently, results from several clinical trials allowed to clarify the impact of anti-inflammatory therapy on short- and long-term outcomes in patients presenting with ACS. CRP, a pentraxin derived hepatically, is a useful downstream

clinical biomarker of the systemic inflammatory response and is considered as a surrogate of upstream cytokines, such as IL-1 and IL-6. The effect of IL-1 receptor antagonist therapy on markers of inflammation in non-ST elevation ACS study (MRC-ILA Heart Study) demonstrated the impact of IL-1 inhibition in inflammatory response reduction in patients presenting with non-ST-segment elevation ACS, showing a decrease of inflammatory biomarkers after 14 days of IL-1 receptor antagonist (Anakinra) administration [16]. On the basis of these results, several following studies have evaluated the IL-1 pathway blockade as a target for controlling the inflammatory response in patients with ACS.

The CANTOS trial, a randomized double blinded study, enrolled 10,061 post-ACS patients with RIR defined as increased hsCRP blood level (≥2 mg/l) who were randomly assigned either to one of three different doses groups of canakinumab (50, 150 and 300 mg, administered subcutaneously every 3 months), a monoclonal antibody targeting IL-1β, or to placebo. The primary efficacy end point included nonfatal MI, nonfatal stroke or cardiovascular death, while the secondary end point was hospitalization for unstable angina requiring urgent revascularization. Both the primary and the secondary end point occurred with a statistically significant lower rate during the 48 months follow-up in the group treated with canakinumab 150 mg, irrespective of aggressive blood cholesterol control [17]. Canakinumab did not change lipid levels, while it resulted in a dose-dependent reduction of hsCRP levels. In a prespecified secondary analysis, canakinumab has been shown to be particularly effective among those who achieved evidence of inflammation reduction, with most of the benefit confined to those who achieved hsCRP <2 mg/l [17].

Another remarkable smaller study evaluating the efficacy of IL-1 pathway blockade is the VCU-ART3 trial [18]. The VCU-ART3 study enrolled 99 STEMI patients to receive either anakinra 100 mg once daily (standard dose), or 100 mg twice daily (high dose) or placebo. The primary end point of this trial was hsCRP area under the curve, which was significantly lower among patients in both anakinra arms compared with placebo. The prespecified secondary end points of the trial showed a significantly decreased occurrence of death, new-onset heart failure and heart failure hospitalization among patients under anakinra in comparison with placebo at 12-month follow-up. In this study, the anakinra group did not experience a significantly higher serious infections incidence.

The CIRT trial, instead, failed in demonstrating the efficacy of low-dose methotrexate (at a target dose of 15–20 mg weekly) in reducing the risk of nonfatal MI, nonfatal stroke or cardiovascular death in comparison with placebo in 4786 patients with a history of ACS or multivessel CAD who additionally had either Type 2 diabetes or the metabolic syndrome [19].

The trial was stopped after a median follow-up of 2.3 years because methotrexate administration showed no beneficial effects in preventing cardiovascular events and no reduction in inflammatory markers blood levels was detected. Furthermore, among the population taking the drug, higher rates of elevated liver-enzyme levels, reduced leukocyte counts and haematocrit level and higher incidence of non-basal-cell skin cancers were registered in comparison with the placebo group. Of note, while in the CANTOS trial were enrolled patients at high RIR with increased baseline hs-CRP blood levels, in the CIRT trial the study population was only required to suffer from either diabetes mellitus or metabolic syndrome. Second, methotrexate has no specific effect on the IL-1β/IL-6/CRP pathway, recognized as a causal meditator in atherosclerosis as for canakinumab.

In the last 2 years, two important randomized double-blind trials, COLCOT and the LoDoCo 2 trial, have evaluated the low dose colchicine in ACS secondary prevention [20,21]. Colchicine is an antirheumatic drug with a wide spectrum of action including NLPR3 inflammasome inhibition and, consequently, IL-1β/IL-6/CRP pathway downregulation [22]. In the COLCOT trial, 4745 patients with history of MI within the previous 30 days were enrolled and randomly assigned either to colchicine 0.5 mg daily or to placebo [20]. The primary composite end point included death from cardiovascular causes, cardiac arrest, MI, stroke or urgent hospitalization for angina leading to coronary revascularization and every component was also analyzed separately. Daily consumption of low dose colchicine was proven to significantly decrease cardiovascular events during a median follow-up of 22.6 months. It is noteworthy that collateral effects like diarrhea and pneumonia occurred more frequently in the colchicine group, even though the difference within the placebo group did not reach the statistical significance. Similarly, relying on the results of the previous LoDoCo trial [23], the LoDoCo2 trial randomized 5522 clinically stable patients with previous MI to receive either a colchicine dose of 0.5 mg daily or placebo [21]. During a median follow-up of 29 months, colchicine significantly reduced the primary end point, a composite of cardiovascular death, nonprocedural MI, ischaemic stroke or ischemia-driven coronary revascularization. Similar to COLCOT, low-dose colchicine was well-tolerated and rates of adverse events were comparable between the two groups. Nonetheless, non-cardiovascular death was more frequent among the patients under colchicine, even if in this group were not detected statistically significantly increased occurrence of serious adverse events in comparison with the placebo-

10.2217/fca-2021-0032

group. Moreover, the results from the ongoing CLEAR-SYNERGY trial (NCT03048825) evaluating the combined use of colchicine and spironolactone in patients presenting with STEMI will hopefully shed light on the role that colchicine should play in the secondary prevention of ACS in patients with recent MI.

Local markers of coronary inflammation

In the recent years, great attention has been given to the role of local coronary inflammation in determining the risk of recurrent ischemic events in patients following an ACS, as to new invasive and noninvasive imaging techniques to early assess local vascular inflammation signs.

Emerging noninvasive approaches include PET/computed tomography (CT) and PET/magnetic resonance (MR). Principal limitations for their use in clinical practice are their relative unexplored predictive value for cardiovascular events, the limited availability and the high costs [24].

Coronary anatomical detection by coronary CT angiography allows for epicardial CAD detection and the phenotypic characterization of the atherosclerotic plaque to detect high-risk features, such as napkin-ring sign, positive remodelling (remodeling index >1.1), low attenuation plaques and spotty calcifications [25]. They do not directly quantify vascular inflammation but may provide relevant additive information on plaque vulnerability that finally precipitate an ACS. In patients undergoing coronary CT angiography, plaque characterization and calcium score have been associated to a ten-folder higher risk of developing an ACS, with a significant contribution in patients reclassification compared with luminal assessment alone [26].

Intracoronary invasive imaging, including intravascular ultrasound (IVUS) and optical coherence tomography (OCT), allowed a more detailed morphological characterization of the atherosclerotic plaque [27–30] and several studies have identified plaque characteristics portending a higher risk of future cardiovascular events (Table 1) [31]. IVUS has a relatively low spatial resolution to detect fibrous cap thickness and a limited ability to identify lipid plaque distribution. Moreover, combining IVUS with near-infrared spectroscopy (NIRS) in a multimodal catheter, is a validated technique for the characterization of coronary plaque structureand composition [32,33]. On the other hand, OCT, with its tenfold higher resolution is able to detect vulnerable thin caps and superficial erosions [34,35] with an excellent correlation with histology [36]. Based on OCT findings, the underlying mechanisms of ACS have been identified *in vivo* (i.e.: plaque rupture, plaque erosion, calcified nodule) [37], and the plaque characteristics (i.e., lipid or fibrous plaque type, presence of macrophages, fibrous cap thickness) have been correlated to increased serum levels of inflammatory biomarkers [38–40] and to different risk of recurrent events [37]. Recent studies demonstrated that the patients presenting with ACS secondary to a plaque rupture as assessed by OCT evaluation at culprit lesion, had a higher incidence of MACE at follow-up compared with those with intact fibrous cap plaque (i.e., plaque erosion) [41], probably as a consequence of macrophage infiltration at the site of plaque rupture [42].Interestingly, macrophage infiltrates have been proven to have a negative prognostic value even in case of plaque erosion, thus endorsing the theory that greater local inflammatory response is related to a more aggressive phenotype of CAD [41,43,44]. Recently, Fracassi *et al.* [45] showed that the combination of high-risk OCT features (defined as plaque rupture, macrophage infiltration and multifocal atherosclerosis) and high CRP levels (≥2 mg/l) has a higher predictive role for ACS recurrence than CPR alone.

In the CLIMA study [46] several OCT features of the atherosclerotic plaque (macrophage infiltration, fibrous cap thickness < associated 75 μm, maximum lipid arc extension >180° and minimum lumen area <3.5 mm2) have been with an increased risk of MACE at follow-up (cardiac death and target segment myocardial infarction). However, in this study, there was no statistically significant difference in hsCRP levels between patients who experienced a clinical event at follow-up and those who did not, probably because both stable and ACS patients were included.

Finally, intracoronary imaging allowed the '*in-vivo*' detection of 'healed plaques' [47]. After an acute plaque destabilization, orchestrated plaque healing prevents the formation of an occlusive thrombus and promotes plaque repair aimed at restoring the integrity of the vessel [48] Recent optical coherence tomography studies showed an association between the presence of healed coronary plaques and higher nontarget lesion, ischemia-driven revascularization rates, in the absence of acute events [48,49]. A better comprehension of predictors of 'favourable' healing may therefore further improve the cardiovascular burden especially in high-risk patients.In conclusion, these data taken together support that a combined evaluation of systemic inflammation and local inflammation with imaging plaque characterization can be complementary in identifying patients at high risk for recurrent events.

Table 1. Intracoronary imaging studies evaluating plaques characteristics that connote a higher risk of cardiovascular events.

Study (year)	Imaging modality	Population	Main purposes	Primary end points	Follow-up	Main findings	Ref.
CLIMA (2020)	OCT	1003 patients undergoing OCT evaluation of untreated proximal LADA in the context of clinically indicated coronary angiogram	Predictive value of high-risk plaque features (MLA, FCT, lipid arc circumferential extension, macrophages)	Composite of nonfatal MI, nonfatal stroke or cardiovascular death	12 months	The simultaneous presence of high-risk OCT plaque features (MLA <3.5 mm^2, FCT <75 μm, lipid arc circumferential extension $>180°$, and OCT-defined macrophages) was associated with a higher risk of major coronary events	[40]
Fracassi *et al.* (2019)	OCT	178 patients admitted for ACS undergoing OCT	Identification of high-risk patients on the basis of OCT features and CRP serum levels as markers of systemic inflammation	Recurrence of ACS	36 months	The combination of systemic inflammation (hsCRP >2 mg/dl) and OCT findings (plaque rupture, macrophage infiltration, multifocal atherosclerosis) in the culprit plaque identifies patients at very high-risk of ACS recurrence	[39]
Massachusetts General Hospital OCT Registry (2020)	OCT	248 patients who underwent OCT imaging during the index procedure and a 6 months follow-up angiography	Identification of predictors of rapid plaque progression that may lead to ACS or SCD	Baseline morphological characteristics and morphological changes from baseline of plaques with rapid progression (defined as a decrease of angiographic MLD $\geq$0.4 mm at follow-up)	7.1 months	Lipid-rich plaques, TCFA and layered plaques were predictors of subsequent rapid plaque progression	[35]
PROSPECT (2011)	IVUS	697 patients with ACS who underwent IVUS imaging after PCI	Identification of IVUS features of culprit or nonculprit lesions associated with MACE at follow-up	Death from cardiac causes, cardiac arrest, MI or rehospitalization due to unstable or progressive angina	40 months	Large plaque burden $>70\%$ (defined as plaque area/EEM area), a small lumen area ($\leq$4.0 mm^2), TCFA morphology were associated with higher recurrence of cardiovascular events	[22]
PREDICTION (2012)	IVUS	506 patients with ACS treated with PCI	Role of local hemodynamic (local shear stress calculated as the product of viscosity and the gradient of blood velocity) and vascular characteristics in coronary plaque progression and to relate plaque changes to clinical events	Predictors of increase in plaque area and decrease in lumen area	12 months	Increase in plaque area was predicted by baseline large plaque burden. Decrease in lumen area was independently predicted by baseline large plaque burden and low endothelial shear stress	[23]
AtheroRemo-IVUS (2014)	IVUS and NIRS	203 patients with SAP or ACS	Long-term prognostic value of NIRS in patients with CAD	Composite of all-cause mortality, nonfatal ACS, stroke, and unplanned coronary revascularization	12 months	CAD patients with an LCBI equal to or above the median of 43.0 had a fourfold risk of adverse cardiovascular events	[24]
PROSPECT ABSORB (2020)	IVUS and NIRS	182 patients presenting MI. Those with a nonobstructive stenosis not intended for PCI but with IVUS plaque burden of $\geq$65% were randomized to treatment with a BVS plus GDMT (n = 93) vs GDMT alone (n = 89)	Outcomes of percutaneous coronary intervention (PCI) of non-flow-limiting vulnerable plaques	The primary powered effectiveness end point was the IVUS-derived MLA at 25-month follow-up. The primary (nonpowered) safety end point was randomized target lesion failure (cardiac death, target vessel-related MI, or clinically driven target lesion revascularization) at 24 months. The secondary (nonpowered) clinical effectiveness end point was randomized lesion-related major adverse cardiac events (cardiac death, MI, unstable angina or progressive angina) at latest follow-up	25 months, clinical follow-up was 4.1 years	PCI of angiographically mild lesions with large plaque burden was safe, substantially enlarged the follow-up MLA, and was associated with favorable long-term clinical outcomes, warranting the performance of an adequately powered randomized trial	[28]

ACS: Acute coronary syndrome; BVS: Bioresorbable vascular scaffold; CBI: Lipid-core burden index; CRP: C-reactive protein; EEM: External elastic membrane; FCT: Fibrous cap thickness; GMDT: Guideline-directed medical therapy; IVUS: Intravascular ultrasound; LADA: Left anterior descending artery; MI: Myocardial infarction; MLA: Minimal lumen area; MLD: Minimal lumen diameter; OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention; SAP: Stable angina pectoris; SCD: Sudden cardiac death; TCFA: Thin-cap fibroatheroma.

10.2217/fca-2021-0032

Conclusion

The role of inflammation in cardiovascular diseases, especially in ACS, has been well established. A residual inflammatory risk persists in approximately a third of all post-acute MI patients, even in patients treated with the more potent anti-thrombotic and lipid-lowering therapies. Targeting residual inflammatory risk is of mainstay importance as RIR is associated with a clinically relevant elevation in the risk of future MI, stroke and all-cause mortality. Recent studies targeting inflammation provided promising results in reduction of atherosclerotic burden, but efforts are still needed for a better understanding of the underlying mechanisms. Finally, further data are warranted to help in identifying the subset of patient who may benefit more from immunomodulatory therapies by promoting a personalized medicine approach.

Future perspective

The CANTOS trial [17] provided a robust confirmation of the inflammatory hypothesis in atherothrombosis by demonstrating that targeting inflammation may lead to a reduction in cardiovascular event rates and paving the way for extensive research in the field of post-acute MI immunomodulation therapy. Several ongoing trials will hopefully shed further light on the potential beneficial effects of the blockade of different pro-inflammatory pathways on secondary prevention of ACS. The CLEAR-SYNERGY trial (NCT03048825) is expected to clarify the role that colchicine should play in the secondary prevention of ACS in patients with recent MI.

Other interesting recently published and ongoing trials are evaluating the effects of other pro-atherosclerotic inflammatory pathways in patients with recent ACS, for example, through the blockade of the 5-lipoxygenase activating protein (Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of Oral AZD5718 in Patients With Coronary Artery Disease; NCT03317002) or of IL-6, such as the recently published ASSAILMI trial. This interesting study by Broch *et al.* showed that the prompt administration of Tocilizumab, a IL-6 blocker, to patients admitted with STEMI within 6 h of symptom onset increased myocardial salvage as assessed by magnetic resonance imaging after 3–7 days [50].

Moreover, the possible beneficial impact of anti-atherosclerotic pathways empowerment has been proposed lately and the ongoing Low Dose Interleukin-2 in Patients With Stable Ischemic Heart Disease and Acute Coronary Syndromes trial (LILACS; NCT03113773) evaluating the effects of low-dose of Proleukin (IL-2) may encourage further researches in potential novel targets for improving clinical outcomes in this setting of patients. Finally, NLRP3 inflammasome blockade using the direct inhibitor OLT1177 (dapansutrile) has already been proven beneficial for myocardial function preservation after ischemia reperfusion injury in mouse [51], but studies in humans are required to clarify if the direct inhibition of this target could be effective in reducing the atherosclerotic burden in patients with previous ACS [52].

Unfortunately, translating the anti-inflammatory effects of these therapies into improvement in clinical outcomes has proven to be challenging and to date, there are no specific anti-inflammatory therapy approved in patients with atherosclerotic cardiovascular disease. CRP is a sensitive but non-specific marker of systemic inflammation, and many different mechanisms may be involved in determining a different risk profile for different patients. Data from invasive and noninvasive imaging techniques demonstrated that characterization of the features of culprit and non-culprit plaques at index procedure in patients with ACS can be used in combination with CRP serum levels for a comprehensive risk stratification of the patient, identifying those who require a closer and intensified secondary prevention [45].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Inflammation plays a key role in atherosclerosis and the persistence of a chronic subclinical inflammation may contribute to atherothrombotic events recurrence.

Define 'residual inflammatory risk'

- Despite optimal medical therapy, patients who suffered from an acute coronary syndrome (ACS) experience a considerable 'residual risk' of a recurrent coronary episode (~30% within the first 3 years).
- Residual cardiovascular risk can be conferred by different factors, including a residual inflammatory risk (RIR) due to an ongoing chronic inflammation, defined as high sensitive C-reactive protein (CRP) ≥2 mg/dl and LDL-C <70 mg/dl.
- Systemic inflammatory biomarkers including CRP, IL-1 and IL-6 have been demonstrated to predict recurrence of ACS and they are widely used to assess and quantify RIR.

Strategies to target RIR

- CANTOS trial demonstrated that targeting inflammation may lead to a reduction in cardiovascular event rates in patents presenting with ACS, opening the way to a post-acute myocardial infarction anti-inflammatory targeted therapy to reduce the RIR.

Local markers of coronary inflammation

- Invasive (optical coherence tomography or intravascular ultrasound) and noninvasive (coronary computed tomography angiography or PET/computed tomography) imaging techniques emerged as new tools providing local markers of coronary inflammation and characterization of high-risk plaques.
- Local biomarkers of coronary inflammation can be used in combination with CRP serum levels in identifying patients at higher RIR who may benefit from an anti-inflammatory targeted therapy.

Future perspective

- The promising results of CANTOS trial provide a confirmation of the inflammatory hypothesis in atherothrombosis, however, the clinical impact of anti-inflammatory therapy for secondary prevention of cardiovascular events is already cause of debate.
- CRP remains a nonspecific marker of systemic inflammation and combination with data from local biomarkers of coronary inflammation may provide a comprehensive risk stratification of patients with RIR.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Ridker PM. Clinician's guide to reducing inflammation to reduce atherothrombotic risk: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* 72(25), 3320–3331 (2018).
2. Piironen M, Ukkola O, Huikuri H *et al.* Trends in long-term prognosis after acute coronary syndrome. *Eur. J. Prev. Cardiol.* 24(3), 274–280 (2017).
3. Price MJ, Berger PB, Teirstein PS *et al.* Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 305(11), 1097–1105 (2011).
4. Bosch J, Eikelboom JW, Connolly SJ *et al.* Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can. J. Cardiol.* 33(8), 1027–1035 (2017).
5. Giugliano RP, Cannon CP, Blazing MA *et al.* Beneft of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Effcacy International Trial). *Circulation* 137(15), 1571–1582 (2018).
6. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation* 138(2), 141–149 (2018).
7. Bohula EA, Giugliano RP, Leiter LA *et al.* Inflammatory and cholesterol risk in the FOURIER trial. *Circulation* 138(2), 131–140 (2018).

•• **In this trial, the authors proved that LDL cholesterol reduction with evolocumab can reduce cardiovascular events among patients with increased blood high-sensitive C-reactive protein (CRP), with greater absolute risk reductions in patients with higher-baseline high-sensitive CRP.**

8. Bohula EA, Giugliano RP, Cannon CP *et al.* Achievement of dual low-density lipoprotein cholesterol and high-sensitivity c-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation* 132(13), 1224–1233 (2015).
9. 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.* 331(7), 417–424 (1994).

• **Liuzzo *et al.* were the first group to prove that high levels of CRP at the the time of hospital admission is related to higher incidence of recurrent ischemia.**

10. James SK, Armstrong P, Barnathan E *et al.* Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: A. GUSTO-IV Substudy. *J. Am. Coll. Cardiol.* 41(6), 916–924 (2003).

10.2217/fca-2021-0032

11. Yang P, Wu P, Liu X *et al.* Association between γ-glutamyltransferase level and cardiovascular or all-cause mortality in patients with coronary artery disease: a systematic review and meta-analysis. *Angioglogy* 70(9), 844–852 (2019).
12. Belcastro E, Franzini M, Cianchetti S *et al.* Monocytes/macrophages activation contributes to b-gamma-glutamyltransferase accumulation inside atherosclerotic plaques. *J. Transl. Med.* 13, 325 (2015).
13. Ndrepepa G, Colleran R, Kastrati A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. *Clin. Chim. Acta* 476, 130–138 (2018).
14. Emdin M, Passino C, Michelassi C *et al.* Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. *Eur. Heart J.* 22(19), 1802–1807 (2001).
15. Niccoli G, Montone RA, Sabato V, Crea F. Role of allergic inflammatory cells in coronary artery disease. *Circulation* 138(16), 1736–1748 (2018).
16. Morton AC, Rothman AMK, Greenwood JP *et al.* The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur. Heart J.* 36(6), 377–384 (2015).
17. Ridker PM, Everett BM, Thuren T *et al.* Anti-inflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* 377(12), 1119–1131 (2017).

•• **The CANTOS trial provided the strong confirmation to the hypothesis that targeting inflammation, and in particular the IL-1β innate immunity pathway, significantly lowers the rate of recurrent cardiovascular events, independently of lipid-level lowering.**

18. Abbate A, Trankle CR, Buckley LF *et al.* Interleukin-1 blockade inhibits the acute inflammatory response in patients with ST-segment-elevation myocardial infarction. *J. Am. Heart Assoc.* 377(12), 1119–1131 (2020).
19. Ridker PM, Everett BM, Pradhan A *et al.* Low-dose methotrexate for the prevention of atherosclerotic events. *N. Engl. J. Med.* 380(8), 752–762 (2019).
20. Tardif JC, Kouz S, Waters DD *et al.* Efficacy and safety of low-dose colchicine after myocardial infarction. *N. Engl. J. Med.* 381(26), 2497–2505 (2019).
21. Nidorf SM, Fiolet ATL, Mosterd A *et al.* Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* 383(19), 1838–1847 (2020).

• **In this trial, the authors proved that low dose colchicine daily consumption significantly lowers the risk of cardiovascular events compared with placebo.**

22. Khambhati J, Engels M, Allard-Ratick M *et al.* Immunotherapy for the prevention of atherosclerotic cardiovascular disease: promise and possibilities. *Atherosclerosis* 276, 1–9 (2018).
23. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. *J. Am. Coll. Cardiol.* 61(4), 404–410 (2013).
24. Cheng VY, Slomka PJ, Le Meunier L *et al.* Coronary arterial 18F-FDG uptake by fusion of PET and coronary CT angiography at sites of percutaneous stenting for acute myocardial infarction and stable coronary artery disease. *J. Nucl. Med.* 53(4), 575–583 (2012).
25. Puchner SB, Liu T, Mayrhofer T *et al.* High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J. Am. Coll. Cardiol.* 64(7), 684–692 (2014).
26. Hou ZH, Lu B, Gao Y, Jiang SL *et al.* Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc. Imaging* 5(10), 990–999 (2012).
27. Zheng B, Mintz GS, McPherson JA *et al.* Predictors of plaque rupture within nonculprit fibroatheromas in patients with acute coronary syndromes the PROSPECT Study. *JACC Cardiovasc. Imaging* 8(10), 1180–1187 (2015).
28. Stone PH, Saito S, Takahashi S *et al.* Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION study. *Circulation* 126(2), 172–181 (2012).
29. Cheng JM, Garcia-Garcia HM, de Boer SPM *et al. In vivo* detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Clinical Trial Eur. Heart J.* 35(10), 639–647 (2014).
30. Niccoli G, Liuzzo G, Montone RA, Crea F. Advances in mechanisms, imaging and management of the unstable plaque. *Atherosclerosis* 233, 467–477 (2014).
31. Montone RA, Niccoli G, Crea F, Jang IK. Management of non-culprit coronary plaques in patients with acute coronary syndrome. *Eur. Heart J.* 41(37), 3579–3586 (2020).
32. Oemrawsingh RM, Cheng JM, García-García HM *et al.* Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. *J. Am. Coll. Cardiol.* 64(23), 2510–2518 (2014).
33. Stone GW, Maehara A, Ali ZA *et al.* Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J. Am. Coll. Cardiol.* 76(20), 2289–2301 (2020).
34. Kubo T, Imanishi T, Takarada S *et al.* Assessment of culprit lesion morphology in acute myocardial infarction. ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J. Am. Coll. Cardiol.* 50(10), 933–939 (2007).

35. Crea F, Libby P. Acute coronary syndromes: the way forward from mechanisms to precision treatment. *Circulation* 136(12), 1155–1166 (2017).

36. Tearney GJ, Regar E, Akasaka T *et al.* Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J. Am. Coll. Cardiol.* 59(12), 1058–1072 (2012).

37. Prati F, Regar E, Mintz GS *et al.* Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur. Heart J.* 31, 401–415 (2020).

38. Niccoli G, Montone RA, Cataneo L *et al.* Morphological-biohumoral correlations in acute coronary syndromes: pathogenetic implications. *Int. J. Cardiol.* 171(3), 463–466 (2014).

39. Montone RA, Camilli M, Del Buono MG *et al.* Brain-derived neurotrophic factor in patients with acute coronary syndrome. *Transl. Res.* 231, 39–54 (2021).

40. Araki M, Yonetsu T, Kurihara O *et al.* Predictors of rapid plaque progression: an optical coherence tomography study. *JACC Cardiovasc. Imaging* doi: 10.1016/j.jcmg.2020.08.014 (2020) (Online ahead of print).

41. Niccoli G, Montone RA, Di Vito L *et al.* Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur. Heart J.* 36(22), 1377–1384 (2015).

42. Scalone G, Niccoli G, Refaat H *et al.* Not all plaque ruptures are born equal: an optical coherence tomography study. *Eur. Heart J. Cardiovasc. Imaging* 18(11), 1271–1277 (2017).

43. Montone RA, Vetrugno V, Camilli M *et al.* Macrophage infiltrates in coronary plaque erosion and cardiovascular outcome in patients with acute coronary syndrome. *Atherosclerosis* 311, 158–166 (2020).

44. Del Buono MG, Montone RA, Iannaccone G *et al.* Diagnostic work-up and therapeutic implications in MINOCA: need for a personalized approach. *Future Cardiol.* 17(1), 149–154 (2021).

45. Fracassi F, Niccoli G, Vetrugno V *et al.* Optical coherence tomography and C-reactive protein in risk stratification of acute coronary syndromes. *Int. J. Cardiol.* 286, 7–12 (2019).

•• **Shows that the combination of systemic evidence of inflammation and optical coherence tomography findings in the culprit plaque identifies very high-risk acute coronary syndrome.**

46. Prati F, Romagnoli E, Gatto L *et al.* Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: The CLIMA study. *Eur. Heart J.* 41(3), 383–391 (2020).

47. Vergallo R, Crea F. Atherosclerotic plaque healing. *N. Engl. J. Med.* 383(9), 846–857 (2020).

48. Russo M, Kim HO, Kurihara O *et al.* Characteristics of non-culprit plaques in acute coronary syndrome patients with layered culprit plaque. *Eur. Heart J. Cardiovasc. Imaging* 21(12), 1421–1430 (2019).

49. Fracassi F, Crea F, Sugiyama T *et al.* Healed culprit plaques in patients with acute coronary syndromes. *J. Am. Coll. Cardiol.* 73(18), 2253–2263 (2019).

• **Shows that there could be an association between the presence of healed coronary plaques, a signature of previous destabilization, and higher non-target lesion, ischemia-driven revascularization rates in the absence of acute events.**

50. Broch K, Anstensrud AK, Woxholt S *et al.* Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J. Am. Coll. Cardiol.* 77(15), 1845–1855 (2021).

51. Toldo S, Mauro AG, Cutter Z *et al.* The NLRP3 inflammasome inhibitor, OLT1177 (dapansutrile), reduces infarct size and preserves contractile function after ischemia reperfusion injury in the mouse. *J. Cardiovasc. Pharmacol.* 73(4), 215–222 (2019).

52. Del Buono MG, Crea F, Versaci F *et al.* NLRP3 inflammasome: a new promising therapeutic target to treat heart failure. *J. Cardiovasc. Pharmacol.* 77(2), 159–161 (2021).