Published in final edited form as:

Atherosclerosis. 2013 July ; 229(1): 18–22. doi:10.1016/j.atherosclerosis.2013.04.004.

Acute Myocardial Infarction Leads to Acceleration of Atherosclerosis

Hui Wang and Daniel T. Eitzman

University of Michigan, Department of Internal Medicine, Cardiovascular Research Center, Ann Arbor, Michigan, USA

Abstract

Patients who experience acute myocardial infarction (AMI) are at increased risk of recurrent events in the weeks to months following the initial event.

The underlying etiology for this vulnerable period following MI is unclear but could be related to the same underlying triggers responsible for the initial MI. Alternatively, the recurrent cardiac event could be promoted by the incident event. For example, several biomarkers reflecting inflammatory activity have been shown to be elevated for weeks to months following MI and this inflammatory response could aggravate existing atherosclerotic lesions by accelerating their growth and/or promoting plaque instability. The purpose of this review is to highlight recent preclinical and clinical studies supporting links between AMI and atherosclerosis and to consider potential therapeutic interventions.

Keywords

inflammatory cytokines; recurrent myocardial infarction; leukocytes

Background

Myocardial infarction (MI) is the leading cause of mortality in many industrialized countries [1]. The substrate for MI is atherosclerosis and MI occurs at the site of pre-existing atherosclerotic lesions, usually following local plaque disruption with subsequent occlusive thrombosis [2]. In general, factors that promote atherosclerosis also promote myocardial infarction [3–8]. While therapeutic targeting of cholesterol with statins has been shown to prevent events and reduce progression of atherosclerosis, it is clear that other lipid-independent factors, such as inflammatory cytokines, also affect progression of atherosclerosis [4, 9]. Atherosclerosis may be considered a chronic inflammatory disease with influx of leukocytes leading to plaque growth [10]. Factors that promote leukocyte proinflammatory activity may therefore lead to progression of atherosclerotic plaques. Identification of conditions in which the likelihood of MI is increased may uncover

Corresponding author: Daniel T. Eitzman, MD, University of Michigan, Cardiovascular Research Center, 7301A MSRB III, 1150 West Medical Center Drive, Ann Arbor, MI 48109-0644, USA, Tel: +1-734-647-9865, Fax: +1-734-936-2641, deitzman@med.umich.edu.

Conflict of interest

None.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

important novel triggers or pathways involved in the progression of atherosclerotic vascular disease.

Epidemiology

Survivors of AMI are at increased risk of subsequent MI [11]. As the initial MI identifies a subset of patients at high vascular risk, it may seem obvious that patients with MI are at higher risk than those without MI. However, the risk of recurrent MI is particularly high shortly after the incident event [11]. In the VALIANT [12] study, recurrent MI was studied in over 10,000 patients who had suffered an initial MI that was associated with left ventricular dysfunction or heart failure [11]. In just over 2 years of follow up, 9.6% (n=861) of patients suffered a recurrent MI. The median time to recurrent MI was 136 days following the initial event. However, the risk for recurrent MI was highest in the first month with the rate markedly declining over the first 3 months. The consequences of recurrent MI are particularly hazardous and in this study the mortality rate was 20.5% within 7 days of the MI. Patients who initially survived the recurrent MI continued to be at high risk for mortality with a greater than two fold increased mortality during the subsequent year compared to patients without recurrent MI. One year mortality was 10.3% for the entire VALIANT cohort while the one year mortality was 38.3% in patients who experienced a recurrent MI. Thus, recurrent MI is common following hemodynamically significant MI's and these recurrent MI's are associated with high mortality rate.

Acute MI and biomarkers of inflammation

A broader understanding of the mechanisms underlying recurrent MI is necessary for application of appropriate therapeutic interventions. Current medical interventions such as statins are highly effective in reducing progression of atherosclerosis and also reducing the risk of recurrent MI [6]. Although contemporary medical treatments have reduced the risk of recurrent ischemic events, the risk remains high. For example, in a study of community dwellers from Olmstead County Minnesota, the risk of a recurrent ischemic event during a 3 year period following a MI was about 44% [13]. However, the risk of recurrent MI occurring after an incident MI occurring in 1998 was 32% lower than for subjects whose incident MI occurred in 1979. The ARIC (Atherosclerosis Risk in Communities) study has also suggested a temporal decline in the risk of recurrent MI [14]. Regardless of the year of the incident MI, the risk of a recurrent MI was particularly high in the first year following the incident MI. The high risk of MI in the weeks to months following an incident MI suggests that the myocardial injury secondary to the acute coronary atherothrombosis may have directly affected the subsequent event. It is also possible that unknown pathways responsible for the incident event are simultaneously affecting other lesions and thus causing a series of temporally related events. Biomarkers reflecting inflammatory activity following MI, including C-reactive protein, serum amyloid A, tumor necrosis factor alpha (TNF- α), CCL2, CCL3, CCL5, CCL18, CXCL8, MIF, C1q/tumor necrosis factor-related protein-3, and others are elevated for days to months following the incident event [15–21] and elevations of many of these predict increased risk of recurrent MI [15, 16]. This inflammatory response, in part secondary to the myocardial injury, could trigger leukocyte influx into atherosclerotic plaques and also promote plaque destabilization.

Preclinical studies suggesting a causal link between AMI and acceleration of vascular disease

To address the direct role of MI on progression of atherosclerosis, preclinical animal studies involving MI with various inflammatory and/or vascular endpoints have been performed. A myocardial proinflammatory response to MI has been well documented in the literature

using preclinical models. In 1998, Ono et al analyzed a rat model of MI [22]. Following induction of MI, TNF- α , interleukin -1 β , and interleukin-6 peaked at 1 week after infarction in the infarct zone and then declined. Gene expression levels of these cytokines in the non-infarcted myocardium remained high up to 20 weeks following the infarct. Although this paper focused on the possible involvement of local cytokine expression towards adverse post-MI remodeling, this myocardial cytokine response could also be responsible for inducing the elevated levels of systemic biomarkers of inflammation reported following MI. The time course is consistent with myocardial expression of cytokines being the origin of the systemic inflammatory response.

The concept that myocardial infarction could affect a vascular process involving an artery remote from the infarct site was demonstrated by Takaoka et al [23]. This paper focused on the potential contribution of MI on coronary restenosis after angioplasty/stenting. Therefore they used a mouse model of femoral artery injury induced by a spring wire to induce a smooth muscle cell-rich lesion characteristic of lesions responsible for restenosis following stent deployment. Neointimal hyperplasia was quantitated 4 weeks following the injury. These authors found that when MI was induced at the time of femoral injury, the neointimal hyperplastic response was augmented. Bone marrow transplantation with marrow from mice expressing green fluorescent protein (GFP) showed that while GFP positive cells contributed to neointimal hyperplasia following the wire injury alone, the marrow contribution was not directly responsible for the AMI-induced increase in lesion area. Using cDNA arrays, they found several proinflammatory transcripts in the injured femoral artery segments that were increased following AMI. Since some of these upregulated genes were TNF- α – responsive, the authors measured TNF- α mRNA from the infarcted hearts and found it to be elevated up to 28 days following the MI. This was associated with increased expression of the TNF receptor (TNFR1) at the site of femoral artery injury. Pentoxifylline treatment, which the authors showed reduced TNF- α synthesis was effective in blocking the effect of AMI on the augmentation of neointima. Thus, this paper importantly demonstrated that inflammatory pathways activated following MI, and probably originating from injured myocardium, were potent enough to accelerate the response to injury at a remote vascular site. Studies in human patients following MI who received coronary stents have demonstrated that a distinct monocyte subset (CD14+CD16+CX3CR1+) is correlated with restenosis within the stented segment [24]. Thus, changes in peripheral blood monocytes following MI may also contribute to adverse vascular events.

Since recurrent CV events following MI most likely reflect effects on the underlying substrate for MI, atherosclerosis, Wright et al tested the impact of AMI in atherosclerotic-prone mice [25]. In this study, apolipoprotein E deficient mice on a western diet underwent induction of anterior MI by LAD ligation. Six weeks later, atherosclerosis was compared between mice with MI and mice that underwent a sham LAD ligation procedure. Mice with experimental MI showed a 65% increase in aortic surface area occupied by atherosclerosis and a 2-fold increase in lesion thickness involving the aortic valves compared to sham-operated mice. Histologically, lesions augmented by MI showed large macrophage rich-areas. Consistent with a role of TNF- α , circulating levels of TNF- α were higher in mice with MI compared to sham-operated mice. To determine whether MI induced changes in leukocytes which might promote leukocyte recruitment to atherosclerotic lesions, leukocyte-endothelial interactions were measured in cremaster venules and found to be increased. Thus, this paper demonstrated that AMI leads to acceleration of atherosclerotic plaque growth and that this is associated with features consistent with enhanced monocyte recruitment.

Most recently, in 2012, Dutta et al [26] studied the effects of MI on atherosclerosis in apolipoprotein E deficient mice. As early as 3 weeks following MI, plaque size had

increased by 50% and this was associated with greater lesion protease activity and greater lesion area occupied by CD11b+ myeloid cells expressing higher levels of inflammatory genes. In mice following MI, monocytes were increased in the blood and spleen for up to 3 months following the MI, with no change in the bone marrow. These changes were also observed in humans that died following AMI. These observations suggested the spleen might be contributing to the post-MI leukocytosis. To specifically determine the role of the spleen in the augmentation of atherosclerosis following MI, splenectomy was performed. This intervention blocked the acceleration of atherosclerosis due to MI. However, hematopoietic stem and progenitor cells (HSPCs) released from the bone marrow appeared to support the spleen-derived monocytosis and acceleration of atherosclerosis. This bone marrow release of HPSCs was associated with evidence of increased sympathetic nervous system activity, presumably activated by the impaired LV function and/or pain following MI. Bone marrow liberation of hematopoietic stem cells had been previously shown to be mediated via the β_3 -adrenoceptor [27]. Accordingly, treatment with a β_3 -adrenoceptor antagonist decreased bone marrow release of HPSCs, reduced splenic output of myeloid cells and reduced inflammatory activity in the atherosclerotic plaques. Thus this study confirmed the effect of AMI on atherosclerosis and elucidated multiple players in a complex sequence of events leading to plaque growth following MI.

Taken together, clinical and preclinical studies support an effect of AMI on proinflammatory cytokines, leukocyte activation, and acceleration of atherosclerosis (See table 1 and figure 1).

Treatment strategies

Currently post-AMI patients with LV dysfunction are typically treated with aspirin, clopidogrel, beta blockers, statins, ACE inhibitors, and aldosterone antagonists [28]. It is likely that these treatments are having protective effects against the proatherogenic stimuli resulting from AMI since many of the pathways shown to be active in the preclinical studies described in this review have been shown to be modified by these drugs. For example aspirin has anti-platelet and anti-inflammatory effects and has been shown to reduce recurrent MI by approximately 25% [29]. Clopidogrel added to aspirin [30] leads to further reduction of recurrent events in the period following AMI. Therapeutic targeting of LDL with statins has consistently shown to reduce recurrent events [31–33]. Higher doses appear to more effective and beneficial effects may not be limited to LDL lowering as statins have also been shown to reduce Crp levels, a biomarker of inflammatory events, independent of LDL lowering [34]. Modulation of other lipid parameters such as free fatty acids, may also be beneficial in the post-MI setting [35]. In some studies, beta blockers have been shown to reduce the risk of recurrent events following MI [36], which may be due to attenuation of the effects of excessive sympathetic nervous system activation. In the COMMIT trial, although there appeared to be a hazard of very early initiation of IV beta blockade (< 24 hours), there was a significant reduction in reinfarction with beta blocker treatment with mean follow up of only 16 days [37]. Beneficial effects of beta blockers following MI may also include reducing LDL susceptibility to oxidation [38]. Heparinoids, given in the acute setting of AMI, may also provide benefits via inhibition of thrombin and by other anti-inflammatory effects [39]. Inhibitors of angiotensin converting enzyme reduce blood pressure and favorably affect ventricular remodeling in left ventricular dysfunction, however, some early studies also demonstrated that ace inhibitors were effective in preventing reinfarction rates. In the SOLVD and SAVE trials, the reduction in recurrent MI rates was approximately 25% [40, 41]. In patients with LV dysfunction following acute MI, antagonists of aldosterone have also been shown to be effective in reducing subsequent cardiovascular endpoints [42].

Thus, the magnitude of the effect on atherosclerosis seen in the preclinical studies described above may not mimic the effects seen in patients treated with modern therapies. Consistent with this concept, the rates of recurrent ischemia following MI have decreased over the past 20 years [13]. However, the period following the acute MI remains a high risk period and recurrent MI is associated with high mortality [11]. Thus, additional therapies are needed to reduce this risk. Although preclinical studies support the hypothesis that myocardial injury is the source of a proinflammatory stimulus leading to acceleration of atherosclerosis, it is also possible that factors responsible for triggering the initial MI are affecting other sites of the coronary tree simultaneously, accounting for the high risk period. This is supported by studies that have shown the presence of multiple plaques with angiographic appearance of recent rupture at the time of acute MI presentation [43, 44]. If this is the case, then the risk of recurrent MI should be similar in patients presenting with unstable angina (i.e. acute plaque rupture without myocardial injury) and those with large MI. Patients who present with unstable angina are generally at lower risk of subsequent ischemic adverse events than those that experience MI. In one study, for example, mortality at 42 days following AMI was highly correlated with the level of troponin elevation [45]. Although the comparison is complex since MI patients are at risk for pump complications due to cardiomyocyte necrosis, and those with high troponin levels are more likely to have completed an infarct in the culprit vessel, it appears that myocardial injury adds significant additional risk for recurrent ischemic events.

Additional therapies designed to target inflammatory pathways following AMI should be tested for prevention of recurrent events during this vulnerable period. Therapy could be limited to several weeks or months following the MI and might be guided by biomarkers reflecting activation of inflammatory pathways. The benefits would have to be weighed against potential adverse consequences of anti-inflammatory therapy. In addition to blocking adaptive immune responses to infectious pathogens, a modest myocardial inflammatory response to injury could play an important role in the healing process. An anti-inflammatory intervention that does not impair myocardial healing but blocks acceleration of atherosclerosis would be ideal. Clinical studies are underway to test the effects of IL-1 β inhibition [46] and low dose methotrexate [47].

References

1. Gersh BJ, Sliwa K, Mayosi BM, et al. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J.* 2010; 31:642–648. [PubMed: 20176800]
2. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. *Eur Heart J.* 2004; 25:1197–1207. [PubMed: 15246637]
3. Hansson GK. Inflammatory mechanisms in atherosclerosis. *J Thromb Haemost.* 2009; 7 (Suppl 1): 328–331. [PubMed: 19630827]
4. Young JL, Libby P, Schonbeck U. Cytokines in the pathogenesis of atherosclerosis. *Thromb Haemost.* 2002; 88:554–567. [PubMed: 12362224]
5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002; 360:7–22. [PubMed: 12114036]
6. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004; 350:1495–1504. [PubMed: 15007110]
7. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004; 291:1071–1080. [PubMed: 14996776]

8. Waters DD, Guyton JR, Herrington DM, et al. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol.* 2004; 93:154–158. [PubMed: 14715339]
9. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2012; 32:2045–2051. [PubMed: 22895665]
10. Tuttolomondo A, Di Raimondo D, Pecoraro R, et al. Atherosclerosis as an inflammatory disease. *Curr Pharm Des.* 2012; 18:4266–4288. [PubMed: 22390643]
11. Thune JJ, Signorovitch JE, Kober L, et al. Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction. *Eur J Heart Fail.* 2011; 13:148–153. [PubMed: 21037250]
12. Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan in acute myocardial infarction trial (VALIANT): rationale and design. *Am Heart J.* 2000; 140:727–750. [PubMed: 11054617]
13. Jokhadar M, Jacobsen SJ, Reeder GS, et al. Sudden death and recurrent ischemic events after myocardial infarction in the community. *Am J Epidemiol.* 2004; 159:1040–1046. [PubMed: 15155288]
14. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med.* 1998; 339:861–867. [PubMed: 9744969]
15. Ridker PM, Rifai N, Pfeffer M, et al. Elevation of tumor necrosis factor- α and increased risk of recurrent coronary events after myocardial infarction. *Circulation.* 2000; 101:2149–2153. [PubMed: 10801754]
16. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1998; 98:839–844. [PubMed: 9738637]
17. Gonzalez-Quesada C, Frangogiannis NG. Monocyte chemoattractant protein-1/CCL2 as a biomarker in acute coronary syndromes. *Curr Atheroscler Rep.* 2009; 11:131–138. [PubMed: 19228487]
18. de Jager SC, Bongaerts BW, Weber M, et al. Chemokines CCL3/MIP1 α , CCL5/RANTES and CCL18/PARC are independent risk predictors of short-term mortality in patients with acute coronary syndromes. *PLoS One.* 2012; 7:e45804. [PubMed: 23029252]
19. Zerneck A, Bernhagen J, Weber C. Macrophage migration inhibitory factor in cardiovascular disease. *Circulation.* 2008; 117:1594–1602. [PubMed: 18362243]
20. Yi W, Sun Y, Yuan Y, et al. C1q/tumor necrosis factor-related protein-3, a newly identified adipokine, is a novel antiapoptotic, proangiogenic, and cardioprotective molecule in the ischemic mouse heart. *Circulation.* 2012; 125:3159–3169. [PubMed: 22653084]
21. Orn S, Breland UM, Mollnes TE, et al. The chemokine network in relation to infarct size and left ventricular remodeling following acute myocardial infarction. *Am J Cardiol.* 2009; 104:1179–1183. [PubMed: 19840558]
22. Ono K, Matsumori A, Shioi T, et al. Cytokine gene expression after myocardial infarction in rat hearts: possible implication in left ventricular remodeling. *Circulation.* 1998; 98:149–156. [PubMed: 9679721]
23. Takaoka M, Uemura S, Kawata H, et al. Inflammatory response to acute myocardial infarction augments neointimal hyperplasia after vascular injury in a remote artery. *Arterioscler Thromb Vasc Biol.* 2006; 26:2083–2089. [PubMed: 16778119]
24. Liu Y, Imanishi T, Ikejima H, et al. Association between circulating monocyte subsets and in-stent restenosis after coronary stent implantation in patients with ST-elevation myocardial infarction. *Circ J.* 2010; 74:2585–2591. [PubMed: 20944435]
25. Wright AP, Ohman MK, Hayasaki T, et al. Atherosclerosis and leukocyte-endothelial adhesive interactions are increased following acute myocardial infarction in apolipoprotein E deficient mice. *Atherosclerosis.* 2010; 212:414–417. [PubMed: 20619838]
26. Dutta P, Courties G, Wei Y, et al. Myocardial infarction accelerates atherosclerosis. *Nature.* 2012; 487:325–329. [PubMed: 22763456]
27. Katayama Y, Battista M, Kao WM, et al. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell.* 2006; 124:407–421. [PubMed: 16439213]

28. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006; 113:2363–2372. [PubMed: 16702489]
29. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; 324:71–86. [PubMed: 11786451]
30. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005; 366:1607–1621. [PubMed: 16271642]
31. LaRosa JC, Deedwania PC, Shepherd J, et al. Comparison of 80 versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the Treating to New Targets [TNT] trial). *Am J Cardiol*. 2010; 105:283–287. [PubMed: 20102935]
32. Tikkanen MJ, Szarek M, Fayyad R, et al. Total cardiovascular disease burden: comparing intensive with moderate statin therapy insights from the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial. *J Am Coll Cardiol*. 2009; 54:2353–2357. [PubMed: 20082922]
33. Murphy SA, Cannon CP, Wiviott SD, et al. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy compared with moderate lipid-lowering statin therapy after acute coronary syndromes from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial. *J Am Coll Cardiol*. 2009; 54:2358–2362. [PubMed: 20082923]
34. Albert MA, Danielson E, Rifai N, et al. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001; 286:64–70. [PubMed: 11434828]
35. Oliver MF. Control of free fatty acids during acute myocardial ischaemia. *Heart*. 2010; 96:1883–1884. [PubMed: 20962339]
36. Freemantle N, Cleland J, Young P, et al. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999; 318:1730–1737. [PubMed: 10381708]
37. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005; 366:1622–1632. [PubMed: 16271643]
38. Croft KD, Dimmitt SB, Moulton C, et al. Low density lipoprotein composition and oxidizability in coronary disease--apparent favourable effect of beta blockers. *Atherosclerosis*. 1992; 97:123–130. [PubMed: 1361323]
39. Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res*. 2008; 122:743–752. [PubMed: 17727922]
40. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet*. 1992; 340:1173–1178. [PubMed: 1359258]
41. Pfeffer MA, Braunwald E, Moya LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial The SAVE Investigators. *N Engl J Med*. 1992; 327:669–677. [PubMed: 1386652]
42. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003; 348:1309–1321. [PubMed: 12668699]
43. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *The New England journal of medicine*. 2000; 343:915–922. [PubMed: 11006367]
44. Tanaka A, Shimada K, Sano T, et al. Multiple plaque rupture and C-reactive protein in acute myocardial infarction. *Journal of the American College of Cardiology*. 2005; 45:1594–1599. [PubMed: 15893172]
45. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *The New England journal of medicine*. 1996; 335:1342–1349. [PubMed: 8857017]

46. Ridker PM, Thuren T, Zalewski A, et al. Interleukin-1beta inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). *Am Heart J*. 2011; 162:597–605. [PubMed: 21982649]
47. Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT). *J Thromb Haemost*. 2009; 7 (Suppl 1):332–339. [PubMed: 19630828]

Figure 1. Acute myocardial infarction (AMI) triggers atherosclerosis and recurrent MI
Systemic inflammatory cytokines (i.e. TNF α , IL-1 β) are elevated following AMI, promoting leukocyte recruitment to atherosclerotic lesions characterized by increased leukocyte-endothelial (L-E) interactions. Haematopoietic stem/progenitor cells are released from bone marrow via activation of sympathetic nervous system (SNS) following AMI and hosted in spleen. Spleen-derived leukocytosis and activation of leukocytes by inflammatory cytokines contribute to the acceleration of atherosclerosis and recurrent MI.

Table 1

Studies for recurrent MI following acute MI

Model	End points	Results	Cytokines	Year	References
Rat MI	Cytokine expression	↑Cytokine expression in infarcted region (1 week) and noninfarcted region (sustained 20 weeks)	↑TNF- α , IL-1 β , and IL-6 in myocardium	1998	Ono, K, et al. [22]
Human MI	Recurrent MI	↑Recurrent MI (75% higher risk in high CRP and SAA group within 20 months after MI)	↑CRP and SAA in plasma	1998	Ridker, PM, et al.[16]
Human MI	Recurrent MI	↑Recurrent MI (3-fold higher risk in high TNF- α group within 20 months after MI)	↑TNF- α in plasma	2000	Ridker, PM, et al.[15]
Mouse MI, femoral artery injury	Neointimal hyperplasia	↑Neointimal hyperplasia (4 weeks after MI)	↑IL-6 in plasma and injured artery, ↑TNF- α in heart	2006	Takaoka, M, et al.[23]
Mouse MI	Atherosclerosis	↑L-E interactions, ↑atherosclerosis (4 weeks after MI)	↑TNF- α in plasma	2010	Wright AP, et al.[25]
Human MI	Recurrent MI, mortality	↑Recurrent MI (9.6% in 2.3 years), ↑mortality (20.5% in 7 days after recurrent MI)		2011	Thune, JJ, et al.[11]
Mouse MI	Atherosclerosis	↑SNS activity, ↑BM-released progenitor cells, monocytopoiesis, ↑atherosclerosis (3 weeks after MI)	↑IL-6 in plaque	2012	Dutta P, et al.[26]