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REVIEW

Emerging strategies to prevent heart failure after myocardial infarction [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Congestive heart failure (CHF) remains a significant cause of death and disability in industrialized countries. Projections show that the prevalence of CHF will increase 46% from 2012 to 2030, resulting in over eight million adults with CHF in the United States. While substantial advances have been achieved in the treatment of CHF over the past two decades, CHF rivals cancer as a cause of mortality. Strategies focused on prevention of CHF should be emphasized to meaningfully impact the projected increase in CHF. Irrespective of the type of CHF, either systolic or diastolic, coronary artery disease has supplanted hypertension as the most prevalent cause for congestive heart failure, with a high rate of mortality and future hospitalizations. Since coronary artery disease plays a central role in the development of CHF, approaches to treat coronary artery disease and identification of patients at risk for recurrent myocardial infarction (RMI) are approaches to prevent development of CHF.

Subjects who sustain recurrent MI represent a particularly high-risk group for development of CHF. Despite the evolution of therapy for MI from thrombolytic therapy to primary percutaneous coronary intervention (PCI), RMI occurs in ~ 10% of patients in the first year after first MI, and 3 years after their first MI. In this review I explore emerging approaches to prevent RMI including the rationale for recent trials of complete revascularization at the time of MI, newly emerging biomarkers that have additive predictive value for identifying patients with high risk of CHF and death when using existing biomarkers. Finally, the paradigm of hematopoietic stem cell mobilization in MI leading to monocyte expansion and acceleration of atherosclerosis is discussed as an emerging approach to identify patients at high risk of RMI, CHF, and death after MI.

Keywords

Coronary, artery, disease, congestive, heart, failure, atherosclerosis, myocardial, infarction, biomarkers, hematopoietic, stem, cells

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Introduction

Coronary artery disease as a leading cause of heart failure

Congestive heart failure (CHF) remains a significant cause of death and disability in industrialized countries¹. It is estimated that 5.1 million Americans over the age of 20 have CHF². Projections show that the prevalence of CHF will increase 46% from 2012 to 2030, resulting in over eight million adults in the United States with CHF². While substantial advances have been achieved in the treatment of CHF over the past two decades, CHF mortality remains as high as cancer mortality^{3,4}. The number of deaths attributable at least in part to CHF was as high in 1995 (287,000 deaths) and in 2010 (279,000 deaths) indicating that while therapies to treat heart failure have improved individual survival, the prevalence of CHF continues to rise². Strategies focused on prevention of CHF should be emphasized to meaningfully impact the projected increase in CHF. Irrespective of the type of CHF⁵, either systolic⁶ or diastolic⁷⁻⁹, coronary artery disease has supplanted hypertension as the most prevalent cause for congestive heart failure, with a high rate of mortality and future hospitalizations. For these reasons, prevention of coronary artery disease events represents an important approach for prevention of CHF in subjects with both reduced and preserved systolic function. While dramatic improvements in treatment for acute coronary syndromes (ACS) has improved survival, studies of new agents to treat ACS should also include CHF as an outcome, as these data are limited relative to standard major adverse cardiac events (MACE) end-points. CHF end-points in clinical trials are more challenging to achieve, as they require prolonged follow-up periods, but would go a long way to begin to understand their impact in prevention of CHF. Since coronary artery disease plays a central role in the development of CHF, approaches under investigation to prevent CHF after MI by reducing recurrent ACS events are discussed below.

Identification of patients with highest risk for progression to heart failure and death after myocardial infarction

A first myocardial infarction (MI) often represents the initial entry to the health care system, and represents an important opportunity for intervention to prevent subsequent cardiovascular disease events and progression to CHF. Patients who suffer MI are at risk for death and illness from several causes including CHF, arrhythmias, sudden death, and recurrent myocardial infarction (RMI). With modern revascularization therapies for MI, often the majority of patients receive prompt revascularization of the infarct related artery, recover to near normal systolic function, and often have minimal symptoms of CHF consistent with what is defined as the American College of Cardiology/American Heart Association (AHA/ACC) Stage B CHF¹⁰. The development of CHF after MI depends on multiple factors. These include the size of the infarct, its location, and if it results in papillary muscle dysfunction causing mitral regurgitation¹¹. Quantitatively, few studies are available reporting the incidence of heart failure after first MI. In Olmstead County Minnesota, 41% of subjects who suffered a prior MI but did not have heart failure at the time of MI developed new onset heart failure 6 years after MI¹². Objective criteria to identify subjects likely to develop CHF 90 days after MI include decreased left ventricular (LV) systolic function, ejection fraction (EF) < 30% after percutaneous revascularization, presentation with Killip class > I,

and Q waves on post-revascularization electrocardiogram (ECG)¹³. Evidence based therapies to improve LV systolic function and prolong life are noted in the ACC/AHA Guideline for the Management of Heart Failure¹⁴. To avoid redundancy and re-iteration of these widely utilized therapies for post-MI heart failure I will briefly summarize the currently accepted medical therapies. Subjects with ST-segment elevation MI treated with primary angioplasty of the infarct-related artery (IRA) with normal ejection fraction should be treated with aspirin 81 mg daily, high intensity statin therapy, and a beta-blocker for 1-year post-MI¹⁵. A P2Y12 inhibitor should be used for a minimum of 1 year. ACE inhibitors are added if there is post-MI LV systolic dysfunction, and an angiotensin receptor blocker may be exchanged if the ACE inhibitor is not tolerated. Aldosterone antagonists (spironolactone or eplerenone) are indicated with post-MI LV systolic dysfunction¹⁴. The sections that follow outline the emerging approaches to prevent progression of atherosclerosis, RMI, and heart failure from MI.

Recurrent MI and heart failure

Subjects who sustain RMI represent a particularly high-risk group for development of CHF. RMI is particularly worrisome as it is associated with a high mortality rate, and high likelihood of CHF in those who survive. Despite the evolution of therapy for MI from thrombolytic therapy to primary percutaneous primary angioplasty (PCI), RMI occurs in ~10% of patients in the first year after first MI, and 3 years after their first MI¹⁶. Of those who sustain a RMI, 40% die within 1 year^{16,17}. Age, diabetes mellitus, unstable angina¹⁷⁻¹⁹, congestive heart failure on admission with MI²⁰ and underlying left ventricular systolic dysfunction²¹ are the strongest clinical predictors of RMI. Amongst medical therapies, ongoing treatment with NSAIDs, and in particular rofecoxib, celecoxib and diclofenac are associated with death and RMI²². Given the high risk of death associated with RMI, and the role of RMI in development of CHF, strategies to prevent its occurrence are an important focus. However, what is remarkably clear throughout the evolution of therapy for MI, patients with CHF and/or left ventricular systolic dysfunction, are at high risk for RMI. Below I will discuss the emerging strategies to prevent RMI with an underlying goal of preventing CHF.

Complete revascularization for prevention of CHF after MI

PCI is the preferred treatment strategy for restoring myocardial perfusion in patients with ST-segment elevation MI²³. Guidelines from both the European Society of Cardiology (ESC) and the ACC/AHA discourage PCI of non-infarct- non-IRA at the time of primary or rescue PCI in stable patients with ST-segment elevation MI (class III recommendation ACC/AHA)²³. This recommendation is based on observation studies and clinical trials with limited power to answer the question of whether there is any benefit in complete revascularization of all coronary lesions > 70% at the time of ST-segment elevation MI. However, multi-vessel coronary artery disease occurs in 40–65% of subjects undergoing PCI for ST-segment elevation MI²⁴⁻²⁷. While reperfusion of the IRA is routinely performed, the presence of critical stenosis in the other coronary vessels can result in ischemia in the non-infarct related territory. Additionally, ST-segment elevation MI is associated with an inflammatory surge that results in plaque rupture in other coronary vessels resulting in

RMI²⁸. Rupture of an unstable coronary-artery plaque that appears to be a single lesion on angiography is commonly deemed the culprit lesion in ST-segment elevation MI. However, patients often harbor multiple complex coronary plaques²⁹. ST-segment elevation MI may represent a pan-coronary process of thin-cap fibroatheromas in non-IRAs³⁰. Plaques in the non-IRA can be responsible for RMI. Therefore, treatment of these other coronary lesions by complete revascularization represents a potentially important approach to prevent progressive myocardial ischemia, RMI, and future CHF.

The concept of complete revascularization in patients with ST-segment elevation MI has been tested in several clinical trials recently, both completed and ongoing. The PRAMI Trial (Controlled Trial number ISRCTN73028481) tested whether performing preventative PCI as part of the procedure to treat the IRA would reduce the combined incidence of death from cardiac causes, non-fatal myocardial infarction, or refractory angina³¹. The PRAMI trial found that the complete revascularization approach reduced death from cardiac causes (hazard ratio versus culprit artery PCI, 0.34), non-fatal myocardial infarction (hazard ratio 0.32), and refractory angina (hazard ratio 0.35) over the standard approach of IRA only PCI³¹. Importantly, the design of PRAMI did not allow for staged PCI of the non-IRA coronary lesions. Heart failure after MI was not an end-point reported by the study. PRAMI importantly did show that complete revascularization at the time of ST-segment elevation MI was feasible and safe. Criticisms of PRAMI were raised regarding the relatively small sample size of the study, raising questions regarding generalizability.

Since the presentation and publication of the PRAMI trial, several other studies have emerged in support of the complete revascularization approach in treatment of ST-segment elevation MI. A similar trial called CVLPRIT (Complete Versus Culprit-Lesion only Primary PCI Trial; ISRCTN2166248) is a randomized prospective trial of 300 subjects³². The study tested if complete revascularization using a staged PCI approach for non-IRA coronary lesions within 45 days after MI versus the IRA only approach reduces all-cause mortality, RMI, heart failure, and need for revascularization on year after enrollment. Secondary end-points included safety end-points including stroke, intracranial hemorrhage, major non-intracranial bleeding, and vascular complications³². The trial results were presented in September 2014 at the European Society of Cardiology meeting and showed a significant reduction in major adverse cardiac events (hazard ratio 0.45, $p < 0.009$). All-cause mortality, RMI and repeat revascularization also showed similar reductions with the staged PCI approach versus infarct artery only approach, but did not reach statistical significance. There was a substantial reduction in heart failure with the staged PCI approach as well (hazard ratio 0.43, $p = 0.14$) but did not reach statistical significance likely due to the small sample patient cohort in the study³³. While the results of the study are encouraging regarding the use of staged PCI for complete revascularization following ST-segment elevation MI, the small study cohort makes the generalizability of the findings questionable.

A recent meta-analysis comparing the benefits and risks of routine IRA-only PCI vs. multi-vessel PCI in ST-segment elevation

MI revealed that multi-vessel PCI during the intervention for ST-segment elevation MI resulted in increased mortality (odds ratio 1.35; $p < 0.001$), but when performed as a staged procedure, hospital mortality was lower (odds ratio 0.35, $p < 0.001$), as well as reduced long-term mortality, and need for repeat PCI with staged, multi-vessel PCI after MI³⁴. The findings support the current view of the ACC/AHA guidelines indicating non-IRA intervention at the time of primary angioplasty for ST-segment elevation MI may be harmful, but also suggest that treatment of severe coronary artery disease without functional testing or assessment of recurrent angina symptoms with staged PCI of the non-IRA lesions may be beneficial. No heart failure related end-points were assessed in the study however.

The COMPLETE Trial (Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease after Primary PCI for STEMI; NCT01740479) is designed to answer the question of complete versus IRA-only revascularization after PCI for ST-segment elevation MI³⁵. The study will recruit 3900 subjects to determine whether opening all suitable narrowings or blockages ($> 70\%$ stenosis or $> 50\%$ stenosis with fractional flow reserve < 0.8) using a staged PCI approach with drug eluting stents of all suitable non-IRA lesions is superior to an IRA-only approach in reducing the composite outcome of death due to cardiovascular causes or RMI. The secondary end-point will be death due to cardiovascular causes, RMI, ischemia-driven revascularization, unstable angina, or heart failure over a 4-year follow-up period.

Completion of this study and others will help determine the efficacy of complete revascularization immediately after MI improves survival. However, the completed and proposed studies of complete revascularization after MI likely do not have an adequate follow-up period to determine if complete revascularization has any impact on heart failure. It would be most useful for a longer follow-up period to be considered in these trials to assess whether the frequency of heart failure is impacted by complete revascularization. Further insights may be gained if more precise heart failure classification is also determined, specifically treatment or admission to hospital for heart failure in subjects with both preserved and reduced systolic function, as both are likely heart failure specific end-points in subjects with prior MI. Findings from such a longitudinal study would potentially have significant impact in the management of patients with MI, and prevent progression to heart failure with either preserved or reduced systolic function over the longer term.

Progression of atherosclerosis after MI: potential target of preventative therapy?

Complete revascularization of critical coronary disease may prevent RMI and CHF. However these studies do not address coronary disease that would not normally be treated, lesions with $< 70\%$ occlusive stenosis of the coronary artery. These non-critical lesions can progress, leading to plaque rupture and RMI. Multiple angiographic studies have documented progression of coronary atherosclerosis after an initial acute coronary syndrome^{36–39}. Importantly, both IRA and non-IRA lesions appear to progress over time. In a very insightful angiographic and intravascular ultrasound based study, the PROSPECT Investigators prospectively evaluated coronary artery disease lesions in 697 patients with acute coronary syndromes

(ACS-Unstable angina, Non-ST segment elevation MI, and ST-segment elevation MI). Subjects were followed for 3–4 years for recurrent coronary disease events including death from cardiac causes, cardiac arrest, myocardial infarction, or unstable angina⁴⁰. Adverse coronary disease events occurred in 20.4% of patients. Remarkably, these subjects had a relatively equal number of culprit lesions in the prior IRA as in the non-IRA. In the non-IRA lesions that caused the coronary event later, the lesions were described as mild, with a mean stenosis of $32.3 \pm 20.6\%$ by conventional angiography on the initial study. However by intravascular ultrasound the same lesions that caused a new event had $> 70\%$ plaque burden, a small luminal area, and were characterized as thin-cap fibroatheromas. This study suggests that after an initial acute coronary syndrome event, significant progression of atherosclerosis occurs in 20% of subjects from angiographically mild appearing lesions, and is as likely to occur in the prior IRA as in non-IRA lesions that would not have been treated during the index catheterization.

In the context of prevention of heart failure and death from recurrent coronary disease events, identification of the small subset of patients who will have recurrent events from recurrent disease in the IRA or non-IRA vessels is critical. In a related study, the PROSPECT investigators evaluated the utility of C-reactive protein (CRP) levels to predict which subjects had a recurrent coronary disease event⁴¹. Subjects with CRP levels that were elevated (3–10 mg/L) or very elevated (> 10 mg/L) 6 months after their index ACS event had greater rates of total and non-IRA coronary events after 3 years than the subjects with normal CRP levels (< 3 mg/L). Elevated CRP levels 6 months after ACS weakly predicted future coronary disease events with a hazard ratio of 1.02. While CRP is a widely utilized measure of inflammation, its use is not widely accepted. Often the results, if elevated, are attributed to non-specific sources such as a wound infection rather than as an index of inflammation that may be tied to coronary artery disease. However, this study highlights the importance of ongoing inflammation in the progression of coronary artery disease, and the principle of using a measure of inflammation to potentially identify subjects at risk for RMI. More specific markers of inflammation that are mechanistically linked to progression of atherosclerosis may be useful in identifying patients at high risk for RMI and CHF.

Emerging biomarkers to identify patients at high risk for CHF and death after MI

Prediction of CHF and death after MI can be based on standard clinical parameters including using the TIMI risk score⁴² or the GRACE score⁴³. However, substantial additional information can be obtained through the use of biomarkers. The value of troponin I, CRP, and brain-derived natriuretic peptide (BNP), in post-ACS risk stratification are well documented⁴⁴. More recently, characterized biomarkers that are predictive of heart failure and death post-MI include growth differentiation factor-15 (GDF-15). GDF-15 is a member of the transforming growth factor- β cytokine superfamily, is induced and secreted from cardiac myocytes during ischemia and stress, and has anti-apoptotic actions⁴⁵. The value of GDF-15 in prediction of death or CHF was tested in a prospective study of 1142 subjects with both non-ST segment elevation and ST-segment elevation MI with a follow-up period of 505 days⁴⁶. GDF-15 levels

were roughly equivalent to N-terminal BNP for prediction of death or CHF after 1 year. However, combining GDF-15 and N-terminal BNP improved the predictive power of either marker alone yielding an AUC C-statistic of 0.81⁴⁶. The value of GDF-15 levels in subjects with ACS was further independently tested by the TIMI group using the PROVE IT-TIMI 22 cohort⁴⁷. They found that GDF-15 levels predicted risk of death, MI, and CHF independent of cardiovascular risk factors, BNP, or CRP levels. Interestingly there was also no significant interaction between GDF-15 levels and intensive statin therapy for risk of death or MI, suggesting statins have minimal effects on GDF-15 levels⁴⁷.

Another recently characterized biomarker of death and CHF after MI is C-terminal proasopressin (copeptin), the C-terminal portion of proasopressin. Arginine vasopressin (antidiuretic hormone) is released from the neurohypophysis to promote water resorption. Copeptin is secreted in equimolar quantities with arginine vasopressin, but is stable in the blood stream, while arginine vasopressin is unstable and rapidly cleared⁴⁸. In the Leicester Acute Myocardial Infarction Peptide (LAMP) Study, the predictive value of copeptin levels to predict death and heart failure in 980 subjects with non-ST and ST-segment elevation MI, and followed for events for 342 days. Copeptin levels were roughly equivalent to N-terminal BNP levels, and prediction of death and CHF were improved when copeptin and N-terminal BNP were combined in the model⁴⁸. The value of copeptin to predict death, RMI, stroke, or resuscitated cardiac arrest was independently tested in the OPTIMAAL cohort in subjects with MI and either clinical CHF or reduced LV systolic function ($EF < 35\%$)⁴⁹. In contrast to the LAMP Study, copeptin was a stronger predictor of mortality compared with either BNP or N-terminal BNP. Collectively, the findings from these two studies highlight additional biomarkers that may be used additively with BNP to identify subjects at risk for death, and for CHF after MI.

A mechanism for acceleration of atherosclerosis after MI

The biological mechanisms underlying RMI remained unclear until recently. A recent study in mice demonstrated that experimental MI or stroke results in enlargement of atherosclerotic lesions with more advanced morphology over weeks after total occlusion of the left coronary artery⁵⁰. Mechanistically, myocardial infarction in mice causes stress and pain, resulting in a surge in release of norepinephrine. Nerves within the bone marrow regulate the release catecholamines⁵¹, which in turn reduce the levels of SDF-1 (CXCL12). Hematopoietic stem (HSC) and progenitor cells (HSPCs) are then released from the bone marrow. In the setting of myocardial infarction HSC and HSPC release dramatically increases rising 2-fold after 6 hours to over 20-fold higher than baseline 3 days into a myocardial infarction⁵⁰. Coinciding with the release of HSCs and HSPCs, monocytes, macrophages, and neutrophils expand within atherosclerotic lesions in the aorta, and are replenished from the blood stream and spleen for up to 3 months after MI in mice. HSPC mobilization requires adrenergic signaling at least initially as HSC and HSPC mobilization was reduced in half by a β_3 adrenergic receptor inhibitor, indicating an immediate effect of the sympathetic nervous system on HSPC mobilization. Similar findings were noted in a small animal model of chronic stress, resulting in mobilization of HSCs and HSPCs and progression

of atherosclerosis⁵². The findings highlight an important new paradigm to verify in human subjects to begin to understand if activation of the HSC/HSPC/Monocyte axis underlies the mechanism of RMI and acceleration of atherosclerosis.

Key differences underlie animal models of MI and humans that seek treatment for MI. In animal models, the left coronary artery, supplying the largest part of the heart, is tied off resulting in necrosis of the anterior wall of the heart. In contrast, human subjects who seek medical attention for MI undergo coronary angiography and revascularization within 90 minutes of admission to hospital. The size and duration of stimulus to mobilize HSPCs in human subjects may be substantially lower than that observed in mice with a completed infarct. However, it is also possible that patients who present late with ST-segment elevation MI may have the most substantial release of HSCs and HSPCs after MI. Human subjects are frequently treated with β_1/β_2 -adrenergic inhibitors after MI, but those with heart failure may be treated with catecholamines (norepinephrine, epinephrine, dopamine, or dobutamine) for blood pressure support if there is heart failure or cardiogenic shock. This may result in more extensive HSC and HSPC mobilization in subjects with CHF after MI, making them at higher risk for RMI. This is only a speculation at this point but will be the subject of further studies.

Despite these important differences between human subjects and animal models of MI, evidence of acceleration of atherosclerosis is still observed after MI in patients. A recent clinical observational study evaluated 449 patients 1 year after STEMI treated by primary angioplasty and β -blockers. One year after MI, 45 patients developed > 70% stenosis in non-IRA vessels⁵³. Most remarkably, the patients that developed critical stenosis in non-IRA arteries had significantly higher levels of epinephrine, norepinephrine and CRP levels 1 year after their index MI⁵³. In a similar prospective observational study, 449 subjects in China with chronic stable angina, non-ST segment elevation and ST-segment elevation MI underwent follow-up coronary angiography 1 year later⁵⁴. One hundred Thirty-four of 449 patients, or 29.8% had some evidence of non-IRA progression of atherosclerosis of varying severity. Over the follow-up period, 52.9% of subjects with ST-segment elevation MI developed progression of atherosclerosis in the non-IRA while 19.6% of subjects with chronic stable angina and non-ST segment elevation MI had evidence of progression of atherosclerosis. Blood was collected 7 days after intervention for retrospective correlation after follow-up angiography. Remarkably, subjects who developed progression of atherosclerosis in the non-IRA had significantly higher levels of monocytes in their blood stream 7 days after their initial procedure. Collectively, the findings of these two studies provide a preliminary indication that the milieu of ST-segment elevation MI 1) elevates catecholamine levels, and 2) monocyte levels that correspond to progression of atherosclerosis 1 year later. While the paradigm of increased adrenergic tone associated with MI mobilizing HSC/HSPCs, monocyte expansion in the spleen and bone marrow, and acceleration of atherosclerosis remains to be validated in human subjects, these studies support this concept.

Further evidence to support this paradigm came from imaging studies using positron emission tomography. Activated inflammatory cells express high levels of glucose transporters and ^{18}F -deoxyglucose is avidly absorbed, facilitating imaging of inflammation⁵⁵. Several recently published studies^{56–58} have made use of this technique to show that ST-segment elevation MI but not chronic stable angina results in a dramatic increase in bone marrow, splenic and vascular inflammatory activity. The findings are supportive of the paradigm of HSC, HSPC and monocyte inflammatory activation by the post-MI milieu. However, it remains unclear if ^{18}F -deoxyglucose imaging of inflammation can be used to identify subjects at high risk of RMI, or predict the development of CHF post-MI.

The paradigm of HSC and HSPC mobilization, monocyte expansion, and acceleration of atherosclerosis in ST-segment elevation MI remains to be verified in human subjects. While HSC and HSPC mobilization and monocyte expansion clearly occurs in animal models of completed, unrevascularized MI, the extent of HSC and HSPC mobilization in human subjects that undergo revascularization and treatment with medical therapy is unclear and requires validation. However, the paradigm and the mediators of HSC and HSPC mobilization and differentiation to monocytes, leading to acceleration of atherosclerosis represents a potential focus to identify patients at risk for RMI, and potentially reduce CHF and death from MI. Therapies directed at HSC and HSPC mobilization and monocyte differentiation may also be a promising approach to reduce acceleration of atherosclerosis after MI, but may also be challenging to administer as these same cell types are also involved in repair of MI.

Conclusions

- MI often leads to CHF, as longitudinal studies show that 40% of subjects with prior MI develop CHF 6 years later.
- RMI occurs in ~10% of subjects after an index ST-segment elevation MI and carries a high mortality rate of 40%. RMI raises the likelihood of developing CHF.
- Complete revascularization of coronary artery disease at the time of ST-segment elevation MI is an emerging approach to prevent RMI.
- Atherosclerosis progresses in 20% of patients after an initial acute coronary syndrome in non-IRA lesions, suggesting improved approaches to identify patients at high risk for progression of coronary disease may prevent RMI and CHF.
- In small animal model experiments, non-revascularized MI results in mobilization of hematopoietic stem and progenitor cells, and expansion of monocytes in the spleen, that contributes to acceleration of atherosclerosis.

- Preliminary studies in human subjects with prior MI also have progression of non-IRA lesions, and subjects who show most substantial lesion progression have elevated levels of catecholamines and higher blood monocyte levels.
- Hematopoietic stem, progenitor cell mobilization, and monocyte expansion in humans with MI have not been studied, but may represent biomarkers for RMI, and potential therapeutic targets to prevent RMI and acceleration of atherosclerosis in non-IRAs.

Author contributions

TRC prepared the manuscript.

Competing interests

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References

- Braunwald E: **Heart Failure**. *JACC Heart Failure*. 2013; 1(1): 1–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Go AS, Mozaffarian D, Roger VL, *et al.*: **Heart disease and stroke statistics--2014 update: a report from the American Heart Association**. *Circulation*. 2014; 129(3): e28–292.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stewart S, MacIntyre K, Hole DJ, *et al.*: **More 'malignant' than cancer? Five-year survival following a first admission for heart failure**. *Eur J Heart Failure*. 2001; 3(3): 315–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stewart S, Ekman I, Ekman T, *et al.*: **Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004)**. *Circ Cardiovasc Qual Outcomes*. 2010; 3(6): 573–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lala A, Desai AS: **The role of coronary artery disease in heart failure**. *Heart Fail Clin*. 2014; 10(2): 353–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mentz RJ, Fiuzat M, Shaw LK, *et al.*: **Comparison of Clinical characteristics and long-term outcomes of patients with ischemic cardiomyopathy with versus without angina pectoris (from the Duke Databank for Cardiovascular Disease)**. *Am J Cardiol*. 2012; 109(9): 1272–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hwang SJ, Melenovsky V, Borlaug BA: **Implications of coronary artery disease in heart failure with preserved ejection fraction**. *J Am Coll Cardiol*. 2014; 63(25 Pt A): 2817–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mentz RJ, Broderick S, Shaw LK, *et al.*: **Heart failure with preserved ejection fraction: comparison of patients with and without angina pectoris (from the Duke Databank for Cardiovascular Disease)**. *J Am Coll Cardiol*. 2014; 63(3): 251–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Rusinaru D, Houpe D, Szymanski C, *et al.*: **Coronary artery disease and 10-year outcome after hospital admission for heart failure with preserved and with reduced ejection fraction**. *Eur J Heart Fail*. 2014; 16(9): 967–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Goldberg LR, Jessup M: **Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction**. *Circulation*. 2006; 113(24): 2851–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Weir RA, McMurray JJ, Velazquez EJ: **Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance**. *Am J Cardiol*. 2006; 97(10A): 13F–25F.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hellermann JP, Jacobsen SJ, Redfield MM, *et al.*: **Heart failure after myocardial infarction: clinical presentation and survival**. *Eur J Heart Fail*. 2005; 7(1): 119–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Frisch DR, Giedrimas E, Mohanavelu S, *et al.*: **Predicting irreversible left ventricular dysfunction after acute myocardial infarction**. *Am J Cardiol*. 2009; 103(9): 1206–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, *et al.*: **2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines**. *Circulation*. 2013; 128(16): e240–327.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bangalore S, Steg G, Deedwania P, *et al.*: **β -Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease**. *JAMA*. 2012; 308(13): 1340–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jernberg T, Hasvold P, Henriksson M, *et al.*: **Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective**. *Eur Heart J*. 2015; pii: ehu505.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Benhorin J, Moss AJ, Oakes D: **Prognostic significance of nonfatal myocardial reinfarction. Multicenter Diltiazem Postinfarction Trial Research Group**. *J Am Coll Cardiol*. 1990; 15(2): 253–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Mueller HS, Forman SA, Menegus MA, *et al.*: **Prognostic significance of nonfatal reinfarction during 3-year follow-up: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II clinical trial. The TIMI Investigators**. *J Am Coll Cardiol*. 1995; 26(4): 900–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- 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(2): 148–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kornowski R, Goldbourt U, Zion M, *et al.*: **Predictors and long-term prognostic significance of recurrent infarction in the year after a first myocardial infarction. SPRINT Study Group**. *Am J Cardiol*. 1993; 72(12): 883–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Orn S, Cleland JG, Romo M, *et al.*: **Recurrent infarction causes the most deaths following myocardial infarction with left ventricular dysfunction**. *Am J Med*. 2005; 118(7): 752–758.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lamberts M, Fosbøl EL, Olsen AM, *et al.*: **Ongoing treatment with non-steroidal anti-inflammatory drugs at time of admission is associated with poorer prognosis in patients with first-time acute myocardial infarction**. *Int J Cardiol*. 168(2): 832–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- O'Gara PT, Kushner FG, Ascheim DD, *et al.*: **2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines**. *Circulation*. 2013; 127(4): e362–425.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jaski BE, Cohen JD, Trausch J, *et al.*: **Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: comparison of single-vessel versus multivessel coronary artery disease**. *Am Heart J*. 1992; 124(6): 1427–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kahn JK, Rutherford BD, McConahay DR, *et al.*: **Results of primary angioplasty for acute myocardial infarction in patients with multivessel coronary artery disease**. *J Am Coll Cardiol*. 1990; 16(5): 1089–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Moreno R, García E, Elizaga J, *et al.*: **[Results of primary angioplasty in patients with multivessel disease]**. *Rev Esp Cardiol*. 1998; 51(7): 547–55.
[PubMed Abstract](#)
- Muller DW, Topol EJ, Ellis SG, *et al.*: **Multivessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group**. *Am Heart J*. 1991; 121(4 Pt 1): 1042–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tanaka A, Shimada K, Sano T, *et al.*: **Multiple plaque rupture and C-reactive**

- protein in acute myocardial infarction. *J Am Coll Cardiol.* 2005; 45(10): 1594–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Goldstein JA, Demetriou D, Grines CL, *et al.*: **Multiple complex coronary plaques in patients with acute myocardial infarction.** *N Engl J Med.* 2000; 343(13): 915–922.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Kubo T, Imanishi T, Kashiwagi M, *et al.*: **Multiple coronary lesion instability in patients with acute myocardial infarction as determined by optical coherence tomography.** *Am J Cardiol.* 2010; 105(3): 318–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Wald DS, Morris JK, Wald NJ, *et al.*: **Randomized trial of preventive angioplasty in myocardial infarction.** *N Engl J Med.* 2013; 369(12): 1115–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Kelly DJ, McCann GP, Blackman D, *et al.*: **Complete Versus culprit-Lesion only Primary PCI Trial (CVLPRI): a multicenter trial testing management strategies when multivessel disease is detected at the time of primary PCI: rationale and design.** *EuroIntervention.* 2013; 8(10): 1190–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. **European Society of Cardiology 2014 Congress.** Press release.
[Reference Source](#)
 34. Bainey KR, Mehta SR, Lai T, *et al.*: **Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: A systematic review and meta-analysis.** *Am Heart J.* 2014; 167(1): 1–14.e2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. **Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE).**
[Reference Source](#)
 36. Waters D, Craven TE, Lespérance J: **Prognostic significance of progression of coronary atherosclerosis.** *Circulation.* 1993; 87(4): 1067–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Kaski JC, Chester MR, Chen L, *et al.*: **Rapid angiographic progression of coronary artery disease in patients with angina pectoris. The role of complex stenosis morphology.** *Circulation.* 1995; 92(8): 2058–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Azen SP, Mack WJ, Cashin-Hemphill L, *et al.*: **Progression of coronary artery disease predicts clinical coronary events. Long-term follow-up from the Cholesterol Lowering Atherosclerosis Study.** *Circulation.* 1996; 93(1): 34–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Kaski JC, Chen L, Chester M: **Rapid angiographic progression of “Target” and “Nontarget” stenoses in patients awaiting coronary angioplasty.** *J Am Coll Cardiol.* 1995; 26(2): 416–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. Stone GW, Maehara A, Lansky AJ, *et al.*: **A prospective natural-history study of coronary atherosclerosis.** *N Engl J Med.* 2011; 364(3): 226–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 41. Kelly CR, Weisz G, Maehara A, *et al.*: **Relation of C-reactive protein levels to instability of untreated vulnerable coronary plaques (from the PROSPECT Study).** *Am J Cardiol.* 2014; 114(3): 376–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. Morrow DA, Antman EM, Charlesworth A, *et al.*: **TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy.** *Circulation.* 2000; 102(17): 2031–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 43. de Araújo Gonçalves P, Ferreira J, Aguiar C, *et al.*: **TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS.** *Eur Heart J.* 2005; 26(9): 865–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Sabatine MS, Morrow DA, de Lemos JA, *et al.*: **Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide.** *Circulation.* 2002; 105(15): 1760–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. Khan SQ, Ng K, Dhillon O, *et al.*: **Growth differentiation factor-15 as a prognostic marker in patients with acute myocardial infarction.** *Eur Heart J.* 2009; 30(9): 1057–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Kempf T, Eden M, Strelau J, *et al.*: **The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury.** *Circ Res.* 2006; 98(3): 351–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. Bonaca MP, Morrow DA, Braunwald E, *et al.*: **Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22.** *Arterioscler Thromb Vasc Biol.* 2011; 31(1): 203–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Khan SQ, Dhillon OS, O'Brien RJ, *et al.*: **C-terminal proavopressin (copeptin) as a novel prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study.** *Circulation.* 2007; 115(16): 2103–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Voors AA, von Haehling S, Anker SD, *et al.*: **C-terminal proavopressin (copeptin) is a strong prognostic marker in patients with heart failure after an acute myocardial infarction: results from the OPTIMAAL study.** *Eur Heart J.* 2009; 30(10): 187–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. Dutta P, Courties G, Wei Y, *et al.*: **Myocardial infarction accelerates atherosclerosis.** *Nature.* 2012; 487(7407): 325–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 51. 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(2): 407–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. Heidt T, Sager HB, Courties G, *et al.*: **Chronic variable stress activates hematopoietic stem cells.** *Nat Med.* 2014; 20(7): 754–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. Wang J, Liu JH, Zhu XL, *et al.*: **Nonculprit Lesion Progression in Patients with ST Elevation Myocardial Infarction After Primary Percutaneous Coronary Intervention.** *Int Heart J.* 2014; 55(1): 48–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
 54. Han Y, Jing J, Tu S, *et al.*: **ST elevation acute myocardial infarction accelerates non-culprit coronary lesion atherosclerosis.** *Int J Cardiovasc Imaging.* 2014; 30(2): 253–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Mulder WJM, Jaffer FA, Fayad ZA, *et al.*: **Imaging and nanomedicine in inflammatory atherosclerosis.** *Sci Transl Med.* 2014; 6(239): 239sr1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 56. Kim EJ, Kim S, Kang DO, *et al.*: **Metabolic activity of the spleen and bone marrow in patients with acute myocardial infarction evaluated by ¹⁸F-fluorodeoxyglucose positron emission tomographic imaging.** *Circ Cardiovasc Imaging.* 2014; 7(3): 454–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
 57. Wollenweber T, Roentgen P, Schaefer A, *et al.*: **Characterizing the inflammatory tissue response to acute myocardial infarction by clinical multimodality noninvasive imaging.** *Circ Cardiovasc Imaging.* 2014; 7(5): 811–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. Emami H, Singh P, MacNabb M, *et al.*: **Splenic Metabolic Activity Predicts Risk of Future Cardiovascular Events: Demonstration of a Cardiosplenic Axis in Humans.** *JACC Cardiovasc Imaging.* 2014.
[PubMed Abstract](#) | [Publisher Full Text](#)

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The 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction¹ changed the recommendation concerning PCI of a non-culprit artery at the time of primary PCI, removing the Class III: Harm designation and replacing it with a Class IIb recommendation (may be considered). Uncertainty remains regarding timing, since, as noted in the article, in some trials multivessel PCI was performed at the time of the initial procedure, and in other trials it was done in a staged fashion prior to hospital discharge. It should be stressed that this recommendation applies to patients selected by trial entry criteria and was not intended to advocate *routine* multivessel PCI in all cases. As such, selection of patients at high risk for recurrent MI, as outlined in the article, remains important. As a minor point, the CVLPRIT trial cited as a presentation in the article has been published.²

The article at points seems to imply that studies that report major adverse cardiac events commonly do not include CHF as an outcome; this is not strictly correct in most cases. While the primary endpoint may include only death, myocardial infarction, and stroke in some trials, hospitalization for CHF is almost always recorded as a secondary endpoint. One challenge is that this latter endpoint is somewhat softer than others since it relies on the decision to admit.

With respect to the proposed studies of complete revascularization after MI, the contention that studies "likely do not have an adequate follow-up period to determine if complete revascularization has any impact on heart failure" is not quite correct. The ongoing COMPLETE trial of 3900 patients cited in the paper has a composite of CV death and new MI as a primary endpoint and a composite of CV death, MI and CHF hospitalization over a 4-year follow-up period as the secondary endpoint. See clinicaltrials.gov for study design.

As noted in the article, identification of patients with residual inflammation after MI may well be important. It may be worth mentioning two ongoing trials of anti-inflammatory therapy in patients with CAD. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) is testing a monoclonal antibody that blocks the inflammatory cytokine interleukin-1 in patients with acute MI and elevated CRP. The Cardiovascular Inflammation Reduction Trial (CIRT) is testing low-dose

methotrexate in patients with stable CAD and either diabetes or metabolic syndrome. See clinicaltrials.gov for details.

Identification of HSC and HSPC mobilization after myocardial infarction could identify a high-risk subgroup, but it is less clear that these cells are the primary actors in acceleration of atherosclerosis. Perhaps they are simply markers of larger infarctions or more severe underlying atherosclerosis. As the article mentions, they may be involved in the healing process, and one would want to be cautious before embarking on an intervention that might potentially interfere with cardiac repair.

References

1. Levine GN, O'Gara PT, Bates ER, Blankenship JC, et al.: 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2015. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, et al.: Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015; **65** (10): 963-72 [PubMed Abstract](#) | [Publisher Full Text](#)

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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Thomas Cimato addresses a key article in identifying the continuum of myocardial infarction leading to heart failure. The odds of a risk factor leading to heart failure is still the highest for myocardial infarction and this is hence a very relevant topic. There are some really minor changes:

1. The statement in introduction “coronary artery disease has supplanted hypertension as the most prevalent cause for congestive heart failure, with a high rate of mortality and future hospitalization” need an appropriate reference for fact check.

To my knowledge based on recent statistics of CHF, CAD and MI have a higher association but by prevalence, HTN is a bigger contributor.

2. There are couple of places where the author states “I will briefly summarize” (5th line, page 2, left column) and “Below I will discuss the emerging strategies.....” (Last line of the paragraph under subheading Recurrent MI and heart failure”. If possible, a reference to self will sound best avoided and a rephrasing to “is summarized” will have a better flow. Otherwise, it’s a well elaborated article reflecting the need for attention in such perfectives post MI.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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