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Left Ventricular Mechanical Dyssynchrony for Optimized Risk Assessment after Acute Myocardial Infarction

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ABSTRACT

Background: Left ventricular ejection fraction (LVEF) is the preferred clinical marker of myocardial function and a predictor of recurrent cardiovascular events following acute myocardial infarction (AMI). However, LVEF is mainly determined by global systolic function while not adequately reflecting other components of cardiac contractility and has, therefore, major limitations as a standalone prognostic marker for post-infarction outcome. Measurement of left ventricular myocardial dyssynchrony may improve risk assessment after AMI, which was subject of the present study.

Methods: A total of 1082 consecutive patients with AMI (STEMI: n=762; NSTEMI: n=320) undergoing cardiac magnetic resonance (CMR) imaging in median 3 days after infarction were included in this multicenter study. Circumferential and radial uniformity ratio estimates (CURE and RURE) were derived from CMR feature-tracking as markers of dyssynchrony (values between 0 and 1 with 1 reflecting perfect synchrony). The clinical study endpoint was the rate of major adverse cardiac events (MACE) at 12 months, consisting of all-cause death, re-infarction, and new congestive heart failure.

Results: Patients with MACE had significantly impaired dyssynchrony estimates ($p<0.001$ for CURE and RURE compared to patients without events). Stratification according to median CURE (0.84) and RURE (0.75) resulted in significantly increased 12-month MACE rates in AMI patients with uniformity ratio estimates below the median ($p=0.001$ in log-rank testing for all). In post-infarction patients with a LVEF >35% (n=959), CURE was identified as an independent predictor of outcome even after adjustment for established prognostic markers ($p=0.011$ in stepwise multivariate Cox regression analysis) while LVEF was not associated with adverse events in this subgroup of AMI patients.

Conclusions: Left ventricular myocardial dyssynchrony is a novel marker for optimized risk assessment after AMI and provides incremental prognostic information particularly in patients with preserved or only moderately reduced LVEF.

ABBREVIATIONS

AMI	Acute myocardial infarction
b-SSFP	Balanced steady-state free precession
CI	Confidence interval
CMR	Cardiac magnetic resonance
CMR-FT	Cardiac magnetic resonance myocardial feature tracking
CURE	Circumferential uniformity ratio estimate
HR	Hazard ratio
IQR	Interquartile range
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
NSTEMI	Non-ST-segment elevation myocardial infarction
RURE	Radial uniformity ratio estimate
STEMI	ST-segment elevation myocardial infarction

INTRODUCTION

Prognosis of patients with acute myocardial infarction (AMI) has significantly improved over the last decades, primarily as a result of advances in interventional and medical treatment options [1]. Nevertheless, AMI survivors still face a substantial risk of recurrent, potentially life-threatening cardiovascular events. Early risk assessment based on clinical characteristics and myocardial function is recommended to further reduce morbidity and mortality following AMI [2, 3]. Left ventricular ejection fraction (LVEF) is a powerful predictor of adverse events and the preferred functional marker for routine risk stratification and therapeutic decision making [2-6]. However, LVEF is mainly determined by global, systolic function while not adequately reflecting other components of cardiac contractility or subtle, focal changes. Furthermore, the majority of AMI survivors maintain a preserved or only moderately reduced LVEF. Consequently, the greatest number of recurrent adverse events occur in these patients despite their lower relative risk compared to the high-risk but small group of patients with severely impaired LVEF. For these reasons, LVEF has major limitations as a standalone parameter for post-infarction outcome and increasing efforts were directed to improve risk stratification beyond sole calculation of LVEF [6]. Cardiac magnetic resonance (CMR) imaging allows detailed visualization of morphological and microvascular alterations after AMI, which provides incremental prognostic information over and above established clinical variables and LVEF [4, 7]. Moreover, CMR myocardial feature tracking (CMR-FT) derived deformation indices emerged as a superior measure of left ventricular (LV) performance and a valuable tool for optimized post-infarction risk assessment [8, 9]. CMR-FT techniques have also been successfully applied for quantification of LV dyssynchrony, another potentially useful prognostic marker in patients with AMI [10-12]. Post-infarction dyssynchrony has been associated with hemodynamic alterations, adverse LV remodeling, and clinical outcome [13-19]. However, the usefulness of LV dyssynchrony for the prediction of future cardiovascular events in AMI survivors has not yet been comprehensively evaluated in an adequately sized multicenter trial. The aim of this study was, therefore, to determine the prognostic value of CMR-FT based assessment of LV dyssynchrony in a large, multicenter AMI population including patients with ST-segment

elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

MATERIAL AND METHODS

Study population

The population of this multicenter CMR study consisted of 1235 patients with AMI participating in 2 randomized trials, the AIDA STEMI (Abciximab Intracoronary versus intravenously Drug Application in STEMI) and the TATORT NSTEMI (Thrombus Aspiration in Thrombus Containing Culprit Lesions in NSTEMI) trial [20-22]. Detailed study protocols and main results have been published previously. In brief, AIDA STEMI randomly assigned patients presenting with STEMI in the first 12 hours after symptom onset to intracoronary or intravenous abciximab bolus during primary percutaneous coronary intervention with subsequent 12-h intravenous infusion in both groups [20]. Consecutive patients at 8 sites in Germany with proven expertise in CMR imaging were enrolled in the CMR substudy (n=795) [21]. The results did not show a difference regarding clinical outcome or CMR parameters of myocardial damage between the treatment groups [20, 21]. The TATORT NSTEMI trial randomized 440 patients with NSTEMI at 7 sites in Germany to investigate the effect of aspiration thrombectomy on microvascular damage in CMR imaging [22]. Compared to standard percutaneous coronary intervention, additional aspiration thrombectomy did not improve reperfusion injury, infarct size, or clinical outcome. Patients in both studies received reperfusion therapy with primary percutaneous coronary intervention and state-of-the-art post-infarction medical treatment according to guideline recommendations [2, 3].

Infarct patients were compared to a control group consisting of 40 consecutive patients who underwent CMR imaging within clinical routine at University Medical Center Göttingen. Patients were eligible as controls provided that cardiac morphology and function did not show any alterations.

The AIDA STEMI (NCT00712101) and the TATORT NSTEMI trial (NCT01612312) were registered with ClinicalTrials.gov and approved by the ethical committees of the participating

sites. This CMR-FT study was supported by a grant from the German Center for Cardiovascular Research and conducted according to the Declaration of Helsiniki. Patients gave written informed consent for study participation.

CMR imaging protocol

All patients underwent CMR imaging on clinical 1.5- or 3.0-T scanners within 10 days after infarction. The standardized protocol has been previously published and included ECG-gated balanced steady-state free precession (b-SSFP) sequences to assess LV function and T1-weighted late gadolinium enhancement images to determine myocardial and microvascular damage [4, 21, 22]. All sequences were acquired in 2- and 4-chamber long-axis views as well as continuous stacks of short-axis slices covering the whole left ventricle. The same CMR protocol was used in all AMI patients and in the control group.

CMR analysis

Infarct characteristics and LVEF were analyzed at a core laboratory by blinded investigators using certified evaluation software (cmr[42], Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada) [4, 21]. All parameters were determined in sequential short-axis planes. Established threshold techniques were applied to assess infarct size and microvascular obstruction as percentage of LV mass.

CMR-FT was performed in an experienced core laboratory at the University Medical Center Göttingen using dedicated software (2D CPA MR, Cardiac Performance Analysis, Version 1.1.2, TomTec Imaging Systems, Unterschleissheim, Germany). Circumferential and radial strain were derived from b-SSFP sequences at basal, midventricular, and apical locations as previously described [9, 23]. In brief, LV endocardial borders were manually traced followed by the application of an automatic border tracking algorithm. Accurate tracking was assured by visual review and manual adjustments, if necessary. Final values were based on the average of 3 independent analyses. Scans that did not allow for a reliable tracking were excluded. Synchrony was evaluated based on the assumption that perfectly synchronous contraction results in equal strain across the myocardium at a given point in time, whereas opposing walls exhibit opposing strains in dyssynchronous hearts. Therefore, circumferential and radial strain

of 48 evenly distributed locations were plotted against spatial positions for each time frame within the respective apical, midventricular and basal slices. Corresponding plots were subjected to Fourier analysis and circumferential (CURE) and radial uniformity ratio estimates (RURE) were calculated per slice with subsequent averaging between spatial locations and then expressed as global myocardial values, as previously described [10, 12, 24]. Resulting values for CURE and RURE range between 0 (corresponding to complete dyssynchrony) and 1 (corresponding to perfect synchrony). The CMR-FT core laboratory in Göttingen has repeatedly proven excellent reproducibility and low inter- and intraobserver variability for strain assessments and synchrony analyses [9, 10, 23].

Clinical endpoints

The clinical endpoint of this study was the 12-month rate of major adverse cardiac events (MACE), consisting of all-cause death, reinfarction, and new congestive heart failure. Each patient contributed only once to the composite endpoint to avoid double counting in case of multiple events per patient (death > reinfarction > new congestive heart failure). A fully blinded clinical endpoints committee adjudicated all events based on data provided by the study sites. More detailed endpoint definitions have been reported previously [20-22].

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables were non-normally distributed in Shapiro-Wilk test and are provided as median with interquartile range (IQR). Comparisons were performed with the chi-square test for categorical data and the nonparametric Mann-Whitney U test for continuous variables. Baseline characteristics and CMR findings are described according to the occurrence of MACE. Furthermore, CURE and RURE were compared to the healthy control group and between patients with STEMI and NSTEMI. Patients were stratified according to median dyssynchrony estimates to assess the composite 12-month MACE endpoint with the Kaplan-Meier method and log-rank testing. Analyses were performed for the overall AMI cohort as well as separately for patients with STEMI and NSTEMI. Predictors of MACE were identified in univariate and stepwise multivariate Cox regression analyses. Hazard ratios (HR) with corresponding 95%

confidence intervals (CI) are provided. All baseline characteristics and CMR findings were considered for univariate analysis. Only significant predictors in univariate analysis (p<0.05) were included in the multivariate model. The clinical endpoint was also assessed in the subgroup of patients with a LVEF >35% using an identical approach. All analyses were performed with SPSS version 23.0 (IBM, Armonk, New York, USA). A 2-tailed p-value <0.05 was considered statistically significant.

RESULTS

Of the 1235 patients with AMI participating in the AIDA STEMI CMR and the TATORT NSTEMI study, 1082 patients had complete CMR protocols with sufficient quality to assess left ventricular dyssynchrony (STEMI: n=762; NSTEMI: n=320 / Figure 1). CMR was performed in median 3 days (IQR 2 to 4 days) after infarction. Follow-up data 12 months after the index event were available in 1080 patients (99.8%) and showed 73 MACE (death: n=32; reinfarction: n=21; congestive heart failure: n=20).

Patient characteristics

Baseline clinical and angiographic characteristics and their association with MACE are illustrated in Table 1. The patient population was predominantly male (75%) with a median age of 63 years (IQR 53 to 72 years). Patients with MACE at 12-month follow-up were significantly older (p<0.001), less often male (p=0.030) or smokers (p=0.015) and had a higher prevalence of hypertension (0.006) and diabetes mellitus (0.006). Furthermore, there were significant differences regarding Killip class on admission (p<0.001) and the number of diseased coronary vessels (p=0.012).

CMR infarct characteristics and dyssynchrony estimates

Structural and functional CMR imaging parameters are provided in Table 2. The median infarct size was 13.3% of LV mass (IQR 5.4 to 21.7%) with a microvascular obstruction zone of 0.4% of LV mass (IQR 0 to 2.0%) and a LV ejection fraction of 50.5% (IQR 43.5 to 57.6%). Uniformity ratio estimates in the overall study population were as follows: CURE 0.84 (IQR 0.75 to 0.89) and RURE 0.75 (IQR 0.67 to 0.83). In comparison, a healthy control group [n=40; 50% male;

median age 64 years (IQR 46 to 76 years); median LVEF 69% (IQR 65 to 72%)] showed significantly higher values for CURE [0.92 (IQR 0.89 to 0.94); p<0.001] and RURE [0.79 (IQR 0.74 to 0.85); p=0.020]. While CURE was similarly reduced in STEMI and NSTEMI [0.83 (IQR 0.75 to 0.89) versus 0.84 (IQR 0.76 to 0.89); p=0.544], RURE was significantly lower in STEMI patients [0.74 (IQR 0.66 to 0.82) versus 0.78 (IQR 0.68 to 0.84); p=0.001]. Patients with MACE had significantly larger infarcts (p=0.001), more microvascular obstruction (p=0.029), a lower LVEF (p<0.001) and lower dyssynchrony estimates (p<0.001 for CURE and RURE / Table 2).

Prognostic value of left ventricular dyssynchrony

Kaplan-Meier plots showing the risk of MACE according to median CURE and RURE in the overall study cohort and in patients with STEMI and NSTEMI are illustrated in Figures 2A and 2B. Uniformity ratio estimates below median were associated with significantly higher 12-month event rates in the overall AMI population and in the subgroup of patients with STEMI. NSTEMI patients with more pronounced dyssynchrony had numerically more MACE with a strong trend towards significance in log-rank testing (p=0.050 for CURE and p=0.067 for RURE). In the overall AMI cohort, CURE and RURE were significantly associated with MACE in univariate Cox regression analysis (p<0.001 for both) but did not add to the profound prognostic implications of age (p=0.002), Killip class (p=0.024) and particularly LVEF (p<0.001) in stepwise multivariate testing (Table 3). However, considering only patients with a LVEF >35% (n=959), CURE was a significant predictor of MACE (p=0.011) in addition to age (p=0.006) and the number of diseased coronary vessels (p=0.015 / Table 4). In contrast, LVEF was no longer independently associated with adverse events in this subgroup of AMI patients with preserved or only moderately reduced LV function. Kaplan-Meier curves according to median dyssynchrony estimates illustrate the prognostic implications of CURE (Figure 3A) while RURE was not predictive for MACE in this subgroup of patients (Figure 3B).

DISCUSSION

The present study is the first to comprehensively assess the prognostic value of LV dyssynchrony determined by CMR-FT in a large, multicenter population of patients with AMI.

The results indicate a significantly higher 12-month MACE rate in case of ventricular dyssynchrony albeit the prognostic implications of LVEF remained superior in the overall study population. In patients with a LVEF >35%, however, LV dyssynchrony emerged as an independent predictor of post-infarction adverse events. Therefore, estimates of LV dyssynchrony enable optimized risk assessment after AMI by expanding and complementing the prognostic significance of LVEF, the preferred functional marker in clinical routine.

Role of CMR for post-infarction risk assessment

According to current guidelines, it is recommended to determine myocardial function as a key prognostic factor in all patients with AMI before hospital discharge [2, 3]. Routine echocardiography with calculation of LVEF is usually the preferred modality due to its wide and easy availability. Nevertheless, CMR imaging allows for a more accurate assessment of LVEF and provides additional insights into post-infarction myocardial and microvascular damage. Numerous trials have repeatedly shown the incremental prognostic information of infarct size and microvascular obstruction beyond established risk factors and thus emphasize the benefits of visualizing the structural changes after AMI [4, 7]. Furthermore, extended CMR protocols with T1 mapping techniques and T2* imaging enable an even more detailed tissue characterization with additional value for prognostication in AMI survivors [25-27]. Most recently, CMR studies also investigated approaches to overcome the drawbacks of sole LVEF calculation for analysis of myocardial function and identified CMR-FT as a promising tool. CMR-FT derived multidirectional myocardial strain emerged as a superior measure of LV performance and a valuable marker for adverse events following AMI over and above LVEF [9]. The current CMR-FT trial focused on LV dyssynchrony, an important aspect of ventricular performance that is not sufficiently reflected in LVEF. Mechanical LV dyssynchrony was associated with adverse outcome in asymptomatic individuals participating in the Multi-Ethnic Study of Atherosclerosis (MESA) and in patients with coronary artery disease [28, 29]. Previous studies in AMI cohorts mainly targeted the prediction of post-infarction LV remodeling while clinical outcome data are sparse and mostly derived from small populations [13-19]. Moreover, these investigations used different imaging modalities to assess synchronicity (e.g. speckle-tracking echocardiography,

single-photon emission computed tomography, or CMR tagging) with known limitations (e.g. image quality and observer dependency, radiation exposure, or time consuming acquisition of additional CMR sequences). In contrast, CMR-FT-derived dyssynchrony estimates are based on high-quality b-SSFP images, which are part of standard CMR protocols. Using this innovative technique, our study proves the association between mechanical LV dyssynchrony and clinical outcome in AMI survivors with independent prognostic implications in patients with a LVEF >35%. The results were driven by significantly higher event rates in STEMI patients with dyssynchronous LV contraction. In contrast, the NSTEMI cohort showed a trend without reaching statistical significance, which might be due to lesser myocardial damage or the lower sample size. With regard to the investigated dyssynchrony estimates, CURE turned out to be more suitable for post-infarction risk assessment compared to RURE. This finding is in line with previous studies, which identified dyssynchrony measures based on circumferential strain as the most robust and reproducible approach [10]. Furthermore, the extent of myocardial injury might also play a role for the superiority of CURE in the overall population with AMI. CURE is already sensitive to subendocardial fibre damage, which can be found in all patients with STEMI and NSTEMI. In contrast, RURE responds after more pronounced, transmural infarction as usually seen in STEMI patients.

Clinical implications and future directions

Currently, LVEF is the only imaging parameter with direct implications for the management of post-infarction patients, e.g. in terms of medical treatment or prophylactic cardioverter-defibrillator implantation. Other functional or morphological CMR parameters have not yet found their role in clinical practice despite proven prognostic relevance in multiple studies and even superiority to sole LVEF-based risk assessment. There are a few factors that may account for this imbalance. First, some clinicians still consider CMR as a complex and time-consuming examination that is restricted to some highly specialized centers. However, contrary to this assumption, local expertise and availability have significantly increased during the last decades and a post-infarction CMR protocol can be acquired in roughly 30 minutes, which only marginally exceeds the duration of a comprehensive transthoracic

echocardiography. Second, the variety of different CMR parameters for risk stratification impedes the clinical use and may be confusing for physicians without advanced CMR knowledge. Risk-scoring models that incorporate several prognostic markers into a simple score have been introduced recently to overcome this drawback [7]. The third and probably most important reason for the slow implementation of CMR-based risk assessment in clinical routine is the lack of studies investigating CMR-guided management approaches in patients with AMI. Despite the proven prognostic value of morphological and functional alterations in CMR imaging, any benefit of considering these findings for treatment decisions remains speculative in the absence of randomized trials. However, the scientific basis to assume improved outcome and to initiate such studies is solid. For instance, current decision-making on post-infarction primary prophylactic cardioverter-defibrillator implantation, which almost exclusively relies on LVEF, is suboptimal. Only a very small portion of patients with implanted devices require interventions after AMI and patients with preserved ventricular function are not considered for device implantation although arrhythmic events are not uncommon in this population [30]. Therefore, additional factors, such as LV dyssynchrony, have a great potential to improve post-infarction arrhythmic risk stratification. Furthermore, LV dyssynchrony might help to prevent adverse remodeling after AMI by enabling a more tailored pharmacological therapy (e.g. aldosterone antagonists in patients with preserved LVEF but dyssynchronous contraction). These and other management approaches deserve further exploration in future studies.

Limitations

The population of this multicenter CMR study was recruited at several sites in Germany using different CMR vendors. However, the scanning protocol was identical in all centers and data analysis was performed centrally in a core laboratory. In the absence of specific recommendations regarding the optimal time of CMR imaging after AMI, scans were performed within several days after the acute event. It cannot be excluded that CMR-FT parameters may change over time due to ongoing remodeling processes, similar to the discussed time-dependency of myocardial edema [31, 32]. Therefore, a later assessment of LV dyssynchrony might have resulted in an even better prediction of future cardiovascular events. Furthermore,

the results of the present study are restricted to stable AMI patients without contraindications to undergo CMR imaging. CMR-FT based assessment of LV dyssynchrony was not compared to other techniques (e.g. CMR tagging or displacement encoding with stimulated echoes) and, finally, reproducibility of CMR-FT analyses in our core laboratory has been reported in several previous publications and was not repeated in the present study [9, 10, 23].

CONCLUSIONS

This large, multicenter study suggests that CMR-FT based assessment of LV dyssynchrony is a novel marker for optimized risk assessment after AMI and provides incremental prognostic information particularly in post-infarction patients with preserved or only moderately reduced LVEF.

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REFERENCES

1. Jernberg T, Johanson P, Held C, Svennblad B, Lindback J, Wallentin L, Swedeheart/Riks HIA. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;**305**(16):1677-84.

2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;**39**(2):119-177.

3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;**37**(3):267-315.

4. Eitel I, Thiele H. Prognostic role of CMR imaging after myocardial infarction. J Am Coll Cardiol 2014;**64**(19):2069.

5. Rouleau JL, Talajic M, Sussex B, Potvin L, Warnica W, Davies RF, Gardner M, Stewart D, Plante S, Dupuis R, Lauzon C, Ferguson J, Mikes E, Balnozan V, Savard P. Myocardial infarction patients in the 1990s--their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study. J Am Coll Cardiol 1996;**27**(5):1119-27.

6. Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? Eur Heart J 2013;**34**(26):1964-71.

7. Stiermaier T, Jobs A, de Waha S, Fuernau G, Poss J, Desch S, Thiele H, Eitel I. Optimized Prognosis Assessment in ST-Segment-Elevation Myocardial Infarction Using a Cardiac Magnetic Resonance Imaging Risk Score. Circ Cardiovasc Imaging 2017;**10**(11).

8. Schuster A, Hor KN, Kowallick JT, Beerbaum P, Kutty S. Cardiovascular Magnetic Resonance Myocardial Feature Tracking: Concepts and Clinical Applications. Circ Cardiovasc Imaging 2016;**9**(4):e004077.

9. Eitel I, Stiermaier T, Lange T, Rommel KP, Koschalka A, Kowallick JT, Lotz J, Kutty S, Gutberlet M, Hasenfuss G, Thiele H, Schuster A. Cardiac Magnetic Resonance Myocardial Feature Tracking for Optimized Prediction of Cardiovascular Events Following Myocardial Infarction. JACC Cardiovasc Imaging 2018.

10. Kowallick JT, Morton G, Lamata P, Jogiya R, Kutty S, Hasenfuss G, Lotz J, Chiribiri A, Nagel E, Schuster A. Quantitative assessment of left ventricular mechanical dyssynchrony using cine cardiovascular magnetic resonance imaging: Inter-study reproducibility. JRSM Cardiovasc Dis 2017;**6**:2048004017710142.

11. Onishi T, Saha SK, Ludwig DR, Onishi T, Marek JJ, Cavalcante JL, Schelbert EB, Schwartzman D, Gorcsan J, 3rd. Feature tracking measurement of dyssynchrony from cardiovascular magnetic resonance cine acquisitions: comparison with echocardiographic speckle tracking. J Cardiovasc Magn Reson 2013;**15**:95.

12. Taylor RJ, Umar F, Moody WE, Meyyappan C, Stegemann B, Townend JN, Hor KN, Miszalski-Jamka T, Mazur W, Steeds RP, Leyva F. Feature-tracking cardiovascular magnetic resonance as a novel technique for the assessment of mechanical dyssynchrony. Int J Cardiol 2014;**175**(1):120-5.

13. Mollema SA, Liem SS, Suffoletto MS, Bleeker GB, van der Hoeven BL, van de Veire NR, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Gorcsan J, 3rd, Bax JJ. Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. J Am Coll Cardiol 2007;**50**(16):1532-40.

14. Nucifora G, Bertini M, Ajmone Marsan N, Scholte AJ, Siebelink HM, Holman ER, Schalij MJ, van der Wall EE, Bax JJ, Delgado V. Temporal evolution of left ventricular dyssynchrony after myocardial infarction: relation with changes in left ventricular systolic function. Eur Heart J Cardiovasc Imaging 2012;**13**(12):1041-6.

15. Shin SH, Hung CL, Uno H, Hassanein AH, Verma A, Bourgoun M, Kober L, Ghali JK, Velazquez EJ, Califf RM, Pfeffer MA, Solomon SD, Valsartan in Acute Myocardial Infarction Trial I. Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both. Circulation 2010;**121**(9):1096-103.

16. Ng AC, Tran da T, Allman C, Vidaic J, Leung DY. Prognostic implications of left ventricular dyssynchrony early after non-ST elevation myocardial infarction without congestive heart failure. Eur Heart J 2010;**31**(3):298-308.

17. Antoni ML, Boden H, Hoogslag GE, Ewe SH, Auger D, Holman ER, van der Wall EE, Schalij MJ, Bax JJ, Delgado V. Prevalence of dyssynchrony and relation with long-term outcome in patients after acute myocardial infarction. Am J Cardiol 2011;**108**(12):1689-96.

18. Chang SA, Chang HJ, Choi SI, Chun EJ, Yoon YE, Kim HK, Kim YJ, Choi DJ, Sohn DW, Helm RH, Lardo AC. Usefulness of left ventricular dyssynchrony after acute myocardial infarction, assessed by a tagging magnetic resonance image derived metric, as a determinant of ventricular remodeling. Am J Cardiol 2009;**104**(1):19-23.

19. Zhang Y, Yip GW, Chan AK, Wang M, Lam WW, Fung JW, Chan JY, Sanderson JE, Yu CM. Left ventricular systolic dyssynchrony is a predictor of cardiac remodeling after myocardial infarction. Am Heart J 2008;**156**(6):1124-32.

20. Thiele H, Wohrle J, Hambrecht R, Rittger H, Birkemeyer R, Lauer B, Neuhaus P, Brosteanu O, Sick P, Wiemer M, Kerber S, Kleinertz K, Eitel I, Desch S, Schuler G. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. Lancet 2012;**379**(9819):923-931.

21. Eitel I, Wohrle J, Suenkel H, Meissner J, Kerber S, Lauer B, Pauschinger M, Birkemeyer R, Axthelm C, Zimmermann R, Neuhaus P, Brosteanu O, de Waha S, Desch S, Gutberlet M, Schuler G, Thiele H. Intracoronary compared with intravenous bolus abciximab application during primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the AIDA STEMI trial. J Am Coll Cardiol 2013;**61**(13):1447-54.

22. Thiele H, de Waha S, Zeymer U, Desch S, Scheller B, Lauer B, Geisler T, Gawaz M, Gunkel O, Bruch L, Klein N, Pfeiffer D, Schuler G, Eitel I. Effect of aspiration thrombectomy on microvascular obstruction in NSTEMI patients: the TATORT-NSTEMI trial. J Am Coll Cardiol 2014;**64**(11):1117-24.

23. Schuster A, Stahnke VC, Unterberg-Buchwald C, Kowallick JT, Lamata P, Steinmetz M, Kutty S, Fasshauer M, Staab W, Sohns JM, Bigalke B, Ritter C, Hasenfuss G, Beerbaum P, Lotz J. Cardiovascular magnetic resonance feature-tracking assessment of myocardial mechanics: Intervendor agreement and considerations regarding reproducibility. Clin Radiol 2015;**70**(9):989-98.

24. Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, Spinelli J, Halperin H, McVeigh E, Kass DA. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. Circulation 2002;**106**(14):1760-3.

25. Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Mahrous A, Ford I, Tzemos N, Sattar N, Welsh P, Radjenovic A, Oldroyd KG, Berry C. Prognostic significance of infarct core pathology revealed by quantitative non-contrast in comparison with contrast cardiac magnetic resonance imaging in reperfused ST-elevation myocardial infarction survivors. Eur Heart J 2016;**37**(13):1044-59.

26. Reinstadler SJ, Stiermaier T, Liebetrau J, Fuernau G, Eitel C, de Waha S, Desch S, Reil JC, Poss J, Metzler B, Lucke C, Gutberlet M, Schuler G, Thiele H, Eitel I. Prognostic Significance of Remote Myocardium Alterations Assessed by Quantitative Noncontrast T1 Mapping in ST-Segment Elevation Myocardial Infarction. JACC Cardiovasc Imaging 2018;**11**(3):411-419.

27. Reinstadler SJ, Stiermaier T, Reindl M, Feistritzer HJ, Fuernau G, Eitel C, Desch S, Klug G, Thiele H, Metzler B, Eitel I. Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging 2018.

28. Fudim M, Fathallah M, Shaw LK, Liu PR, James O, Samad Z, Piccini JP, Hess PL, Borges-Neto S. The Prognostic Value of Diastolic and Systolic Mechanical Left Ventricular Dyssynchrony Among Patients With Coronary Heart Disease. JACC Cardiovasc Imaging 2018.

29. Sharma RK, Volpe G, Rosen BD, Ambale-Venkatesh B, Donekal S, Fernandes V, Wu CO, Carr J, Bluemke DA, Lima JA. Prognostic implications of left ventricular dyssynchrony for major adverse cardiovascular events in asymptomatic women and men: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2014;**3**(4).

30. Buxton AE, Ellison KE, Lorvidhaya P, Ziv O. Left ventricular ejection fraction for sudden death risk stratification and guiding implantable cardioverter-defibrillators implantation. J Cardiovasc Pharmacol 2010;**55**(5):450-5.

31. Fernandez-Jimenez R, Sanchez-Gonzalez J, Aguero J, Garcia-Prieto J, Lopez-Martin GJ, Garcia-Ruiz JM, Molina-Iracheta A, Rossello X, Fernandez-Friera L, Pizarro G, Garcia-Alvarez A, Dall'Armellina E, Macaya C, Choudhury RP, Fuster V, Ibanez B. Myocardial edema after ischemia/reperfusion is not stable and follows a bimodal pattern: imaging and histological tissue characterization. J Am Coll Cardiol 2015;**65**(4):315-323.

32. Stiermaier T, Thiele H, Eitel I. Early myocardial edema after acute myocardial infarction is stable and not bimodal in humans - Evidence from a large CMR multicenter study. Int J Cardiol 2017;**246**:87-89.

Table 1 Baseline characteristics

Variable	All patients (n=1082)	MACE (n=73)	No MACE (n=1007)	*p*
Age (years)	63 (53, 72)	72 (61, 77)	63 (52, 72)	<0.001
Male sex	811/1082 (75.0)	47/73 (64.4)	763/1007 (75.8)	0.030
Cardiovascular risk factors				
Current Smoking	432/1002 (43.1)	19/66 (28.8)	412/934 (44.1)	0.015
Hypertension	767/1080 (71.0)	62/73 (84.9)	703/1005 (70.0)	0.006
Hyperlipoproteinemia	410/1074 (38.2)	25/73 (34.2)	384/999 (38.4)	0.477
Diabetes mellitus	246/1080 (22.8)	26/73 (35.6)	219/1005 (21.8)	0.006
Body mass index (kg/m^2)	27.4 (25.0, 30.4)	27.0 (25.2, 31.0)	27.4 (24.9, 30.3)	0.899
Previous myocardial infarction	75/1080 (6.9)	5/73 (6.8)	69/1005 (6.9)	0.996
Previous PCI	90/1081 (8.3)	5/73 (6.8)	84/1006 (8.3)	0.653
Previous CABG	20/1081 (1.9)	2/73 (2.7)	18/1006 (1.8)	0.561
ST-segment elevation	762/1082 (70.4)	51/73 (69.9)	711/1007 (70.6)	0.893
Time from symptom onset to PCI hospital admission* (min)	180 (109, 317)	191 (116, 363)	180 (109, 310)	0.397
Door-to-balloon time* (min)	30 (22, 42)	28 (24, 40)	30 (22, 42)	0.497
Killip class on admission				<0.001
1	964/1082 (89.1)	49/73 (67.1)	913/1007 (90.7)	
2	80/1082 (7.4)	15/73 (20.5)	65/1007 (6.5)	
3	21/1082 (1.9)	4/73 (5.5)	17/1007 (1.7)	
4	17/1082 (1.6)	5/73 (6.8)	12/1007 (1.2)	
Number of diseased vessels				0.012
1	541/1082 (50.0)	26/73 (35.6)	514/1007 (51.0)	
2	327/1082 (30.2)	24/73 (32.9)	303/1007 (30.1)	
3	214/1082 (19.8)	23/73 (32.5)	190/1007 (18.9)	
Infarct related artery				0.109
Left anterior descending	443/1082 (40.9)	39/73 (53.4)	404/1007 (40.1)	
Left circumflex	218/1082 (20.1)	13/73 (17.8)	203/1007 (20.2)	
Left main	6/1082 (0.6)	1/73 (1.4)	5/1007 (0.5)	
Right coronary artery	408/1082 (37.7)	19/73 (26.0)	389/1007 (38.6)	
Bypass graft	7/1082 (0.6)	1/73 (1.4)	6/1007 (0.6)	
TIMI flow grade before PCI				0.617
0	550/1082 (50.8)	42/73 (57.5)	507/1007 (50.3)	
1	121/1082 (11.2)	5673 (8.2)	115/1007 (11.4)	
2	216/1082 (20.0)	12/73 (16.4)	203/1007 (20.2)	
3	195/1082 (18.0)	13/73 (17.8)	182/1007 (18.1)	
TIMI flow grade post PCI				0.650
0	20/1082 (1.8)	1/73 (1.4)	19/1007 (1.9)	
1	21/1082 (1.9)	2/73 (2.7)	19/1007 (1.9)	
2	82/1082 (7.6)	8/73 (11.0)	74/1007 (7.3)	
3	959/1082 (88.6)	62/73 (84.9)	895/1007 (88.9)	
Concomitant medications				
Aspirin	1080/1082 (99.8)	73/73 (100)	1005/1007 (99.8)	0.703
Clopidogrel/prasugrel/ticagrelor	1082/1082 (100)	73/73 (100)	1007/1007 (100)	-
Beta-blocker	1032/1080 (95.6)	71/73 (97.3)	959/1005 (95.4)	0.462
ACE inhibitor/AT-1 antagonist	991/1080 (91.8)	69/73 (94.5)	921/1005 (91.6)	0.386
Aldosterone antagonist	140/1080 (13.0)	22/73 (30.1)	118/1005 (11.7)	<0.001
Statin	10321080 (95.6)	70/73 (95.9)	960/1005 (95.5)	0.883

Data presented as n/N (%) or median (IQR). P-values were calculated for the comparison between patients with and without MACE

*only assessed in STEMI patients (n=795)

CABG = coronary artery bypass graft; MACE = major adverse cardiac event; PCI = percutaneous coronary intervention; TIMI = Thromboylsis In Myocardial Infarction

Table 2 Cardiac magnetic resonance imaging results

Variable	All patients	MACE	No MACE	*p*
Infarct size (% LV)	13.3 (5.4, 21.7)	20.4 (9.3, 28.9)	13.1 (5.3, 21.3)	0.001
Microvascular obstruction (% LV)	0.4 (0, 2.0)	1.1 (0, 3.2)	0.3 (0, 1.9)	0.029
LV ejection fraction (%)	50.5 (43.5, 57.6)	40.0 (33.0, 51.9)	50.9 (44.3, 57.6)	<0.001
LV enddiastolic volume (ml)	143 (116, 171)	145 (122, 170)	143 (116, 171)	0.820
LV endsystolic volume (ml)	70 (53, 91)	86 (61, 110)	69 (53, 89)	0.001
CURE	0.84 (0.75, 0.89)	0.76 (0.67, 0.86)	0.84 (0.76, 0.89)	<0.001
RURE	0.75 (0.67, 0.83)	0.69 (0.60, 0.79)	0.76 (0.67, 0.83)	<0.001

Data presented as n/N (%) or median (IQR). P-values were calculated for the comparison between patients with and without MACE.
CURE = circumferential uniformity ratio estimate, LV = left ventricular, % LV = percentage of left ventricular mass, MACE = major adverse cardiac event, RURE = radial uniformity ratio estimate

Table 3 Predictors of MACE in univariate and multivariate Cox regression analysis

Variable	Univariate		Stepwise multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.05 (1.03-1.07)	<0.001	1.04 (1.02-1.07)	0.002
Male sex	0.59 (0.37-0.96)	0.032	-	-
Current smoking	1.90 (1.12-3.24)	0.018	-	-
Diabetes mellitus	1.93 (1.20-3.12)	0.007	-	-
Hypertension	2.36 (1.24-4.48)	0.009	-	-
Killip class on admission	2.04 (1.61-2.58)	<0.001	1.47 (1.05-2.04)	0.024
Number of diseased vessels	1.51 (1.15-2.00)	0.004	-	-
LV ejection fraction (%)	0.94 (0.92-0.96)	<0.001	0.94 (0.92-0.97)	<0.001
Infarct size (% LV)	1.03 (1.01-1.05)	<0.001	-	-
Microvascular obstruction (% LV)	1.09 (1.03-1.15)	0.003	-	-
CURE	0.00 (0.00-0.02)	<0.001	-	-
RURE	0.02 (0.00-0.15)	<0.001	-	-

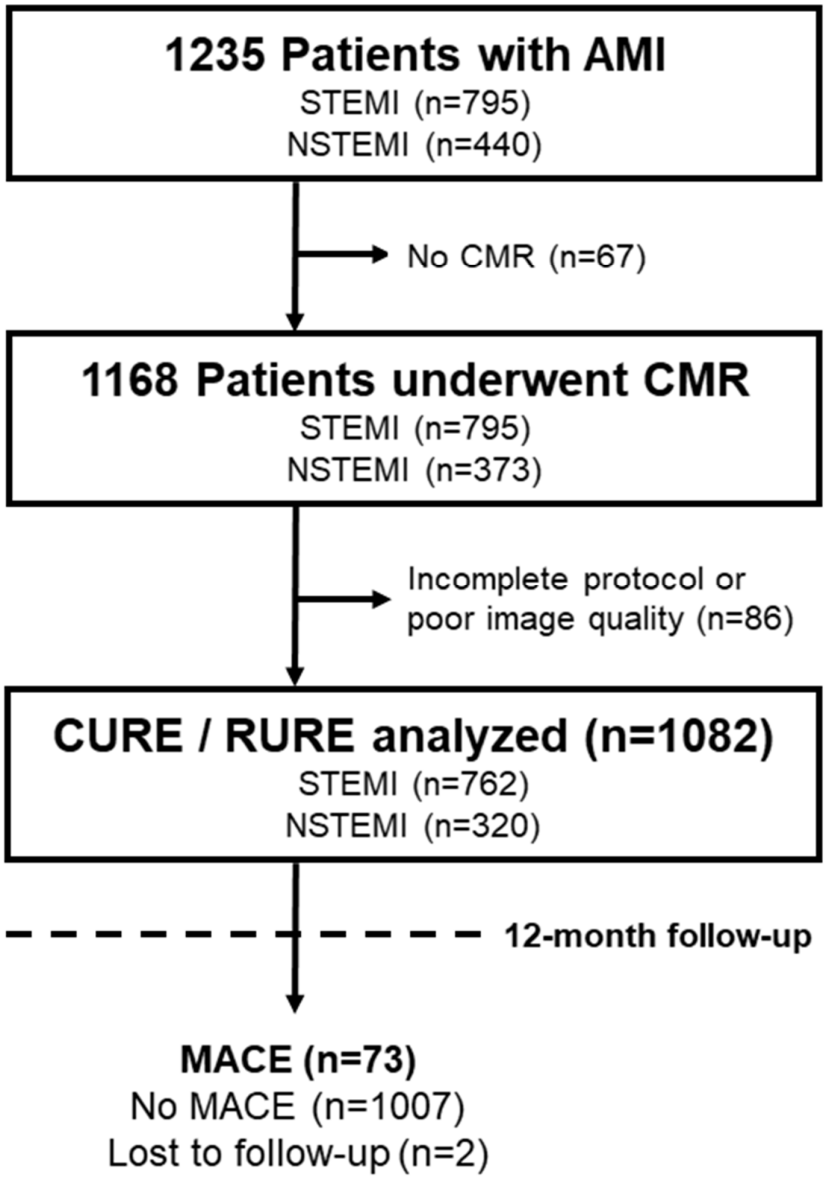
95% CI = confidence interval, CURE = circumferential uniformity ratio estimate, HR = hazard ratio, LV = left ventricular, % LV = percentage of left ventricular mass, RURE = radial uniformity ratio estimate

Table 4 Predictors of MACE in patients with an ejection fraction >35%

Variable	Univariate		Stepwise multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.05 (1.02-1.08)	<0.001	1.04 (1.01-1.07)	0.006
Male sex	0.53 (0.30-0.96)	0.035	-	-
Current smoking	2.17 (1.09-4.32)	0.027	-	-
Diabetes mellitus	2.75 (1.55-4.86)	0.001	-	-
Hypertension	2.14 (1.00-4.58)	0.049	-	-
Killip class on admission	1.87 (1.33-2.63)	<0.001	-	-
Number of diseased vessels	1.59 (1.13-2.24)	0.009	1.61 (1.10-2.37)	0.015
LV ejection fraction (%)	0.96 (0.92-0.99)	0.013	-	-
Infarct size (% LV)	1.03 (1.00-1.05)	0.029	-	-
CURE	0.01 (0.00-0.08)	<0.001	0.02 (0.00-0.39)	0.011

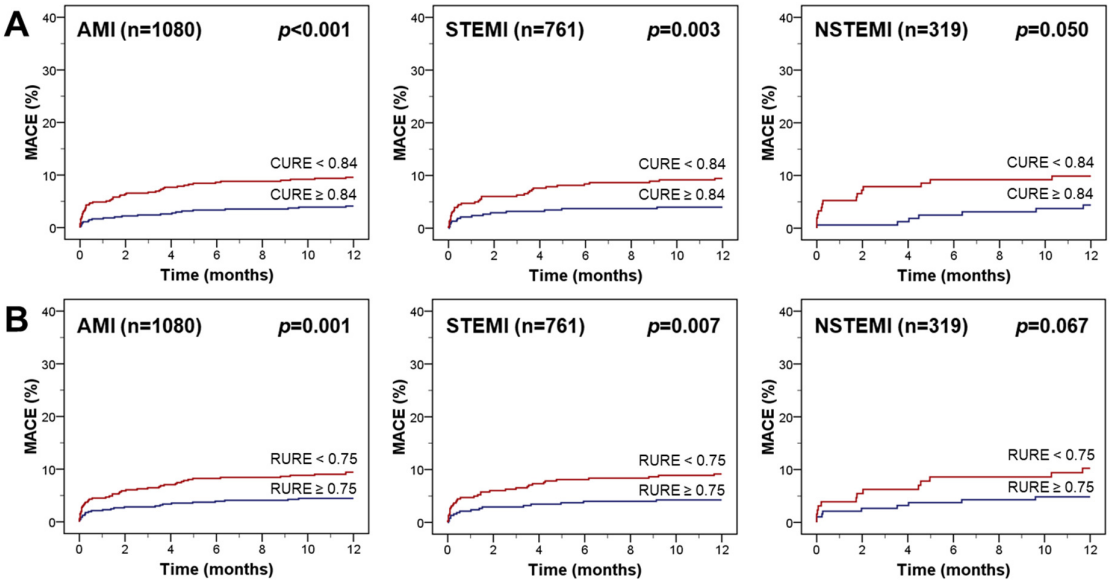
95% CI = confidence interval, CURE = circumferential uniformity ratio estimate, HR = hazard ratio, LV = left ventricular, % LV = percentage of left ventricular mass

Figure 1 Study flow chart



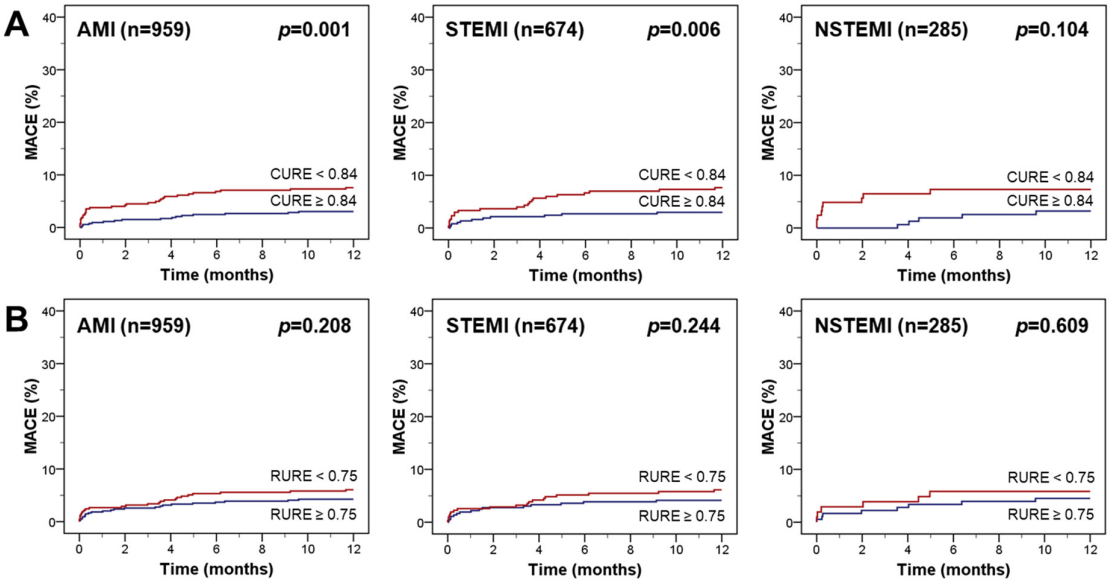
AMI = acute myocardial infarction, CMR = cardiac magnetic resonance, CURE = circumferential uniformity ratio estimate, MACE = major adverse cardiac events, NSTEMI = non-ST-segment elevation myocardial infarction, RURE = radial uniformity ratio estimate, ST = ST-segment elevation myocardial infarction

Figure 2 Kaplan-Meier plots according to median uniformity ratio estimates



AMI = acute myocardial infarction, CURE = circumferential uniformity ratio estimate, MACE = major adverse cardiac events, NSTEMI = non-ST-segment elevation myocardial infarction, RURE = radial uniformity ratio estimate, ST = ST-segment elevation myocardial infarction

Figure 3 Kaplan-Meier plots according to median uniformity ratio estimates in patients with an ejection fraction >35%



AMI = acute myocardial infarction, CURE = circumferential uniformity ratio estimate, MACE = major adverse cardiac events, NSTEMI = non-ST-segment elevation myocardial infarction, RURE = radial uniformity ratio estimate, ST = ST-segment elevation myocardial infarction