


# BMJ Open MRI for measuring therapy efficiency after revascularisation in ST-segment elevation myocardial infarction: a systematic review and meta-regression analysis

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## ABSTRACT

**Objective** To summarise existing data on the relation between the time from symptom onset until revascularisation (time to reperfusion) and the myocardial salvage index (MSI) calculated as proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI after ST-segment elevation myocardial infarction (STEMI).

**Methods** Studies including patients with revascularised STEMI and stating both the time to reperfusion and the MSI measured by T2-weighted and T1-weighted late gadolinium enhancement MRI were searched in MEDLINE, EMBASE and ISI Web of Science until 16 May 2020. A mixed effects model was used to evaluate the relation between the time to reperfusion and the MSI. The gender distribution and mean age in included patient groups, the timing of MRI, used MRI sequences and image interpretation methodology were included in the mixed effects model to explore between-study heterogeneity.

**Results** We included 38 studies with 5106 patients. The pooled MSI was 42.6% (95% CI: 38.1 to 47.1). The pooled time to reperfusion was 3.8 hours (95% CI: 3.5 to 4.0). Every hour of delay in reperfusion was associated with an absolute decrease of 13.1% (95% CI: 11.5 to 14.6;  $p < 0.001$ ) in the MSI. Between-study heterogeneity was considerable ( $\sigma^2 = 167.8$ ). Differences in the gender distribution, timing of MRI and image interpretation among studies explained 45.2% of the between-study heterogeneity.

**Conclusions** The MSI on T2-weighted and T1-weighted late gadolinium enhancement MRI correlates inversely with the time to reperfusion, which indicates that cardioprotection achieved by minimising the time to reperfusion leads to a higher MSI. The analysis revealed considerable heterogeneity between studies. The heterogeneity could partly be explained by differences in the gender distribution, timing and interpretation of MRI suggesting that the MRI-assessed MSI is not only influenced by cardioprotective therapy but also by patient characteristics and MRI parameters.

## Strengths and limitations of this study

- A comprehensive search in three electronic databases was performed and a large number of studies could be included.
- State-of-the-art statistical tests for meta-regression analyses were applied.
- Data on T2-weighted and T1-weighted mapping MRI, which is a valuable and increasingly used alternative to conventional T2-weighted and T1-weighted late gadolinium enhancement MRI for quantifying oedematous and fibrotic myocardium, are not included in the meta-regression analysis.

## INTRODUCTION

Despite a rising incidence of myocardial infarction worldwide, a reduction in mortality has been observed in industrialised nations.<sup>1</sup> This reduction is attributable to salvage of myocardium by therapeutic reopening of culprit arteries using either percutaneous coronary intervention or fibrinolysis.<sup>2</sup> Salvaged myocardium is defined as the difference in size between the previously ischaemic area at risk distal to the obstructed coronary artery and the final infarct size.<sup>3</sup> Quantification of salvaged myocardium after revascularisation therapy allows evaluation of therapeutic efficiency and can be used as an outcome parameter in studies that investigate cardioprotective strategies.<sup>3 99mTc</sup> Technetium-sestamibi single-photon emission tomography (SPECT) is currently the reference standard for quantification of salvaged myocardium.<sup>3</sup> Unfortunately, there are several disadvantages that limit its use. SPECT involves radiation exposure and is logistically demanding since it requires constant availability of the tracer and requires two examinations at different points in time. The tracer has to be injected prior to revascularisation to measure the area

at risk and 1 month after revascularisation to measure the final infarct size.<sup>3</sup>

MRI has been investigated as an alternative method to quantify salvaged myocardium that is logistically easier to perform, involves no radiation exposure, can be performed in a single examination<sup>3</sup> and enables a unique integration of myocardial pathology and measures of myocardial function, such as myocardial strain.<sup>4</sup> The widely accepted MRI techniques of T1-weighted late gadolinium enhancement for measuring necrotic tissue and T2-weighted MRI for identifying oedematous tissue<sup>5</sup> are combined and used to quantify salvaged myocardium based on the assumptions that myocardial necrosis on T1-weighted late gadolinium enhancement MRI can be used to delineate the final infarct size, and that myocardial oedema on T2-weighted MRI can be used to delineate the previously ischaemic area at risk.<sup>6</sup> However, the latter assumption has been a subject of controversial discussion.<sup>7,8</sup> While the results of some studies suggest that the area at risk can be delineated by measuring myocardial oedema on T2-weighted MRI,<sup>9-13</sup> other studies contradict these findings.<sup>14-19</sup> A panel of experts in the field of postmyocardial infarction MRI recently concluded that oedema on MRI after myocardial infarction should be seen as manifestation of myocardial injury induced by ischemia and reperfusion rather than the previously ischaemic area at risk.<sup>20</sup>

The purpose of this meta-regression analysis was to summarise existing data on the relation between the time from symptom onset until revascularisation (time to reperfusion) and the myocardial salvage index (MSI) calculated as proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI after ST-segment elevation myocardial infarction (STEMI).

## MATERIALS AND METHODS

Reporting of this systematic review and meta-regression analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.<sup>21</sup>

### Inclusion and exclusion criteria, search strategy and data extraction

Included studies had to fulfil the following inclusion criteria: (1) STEMI in all study patients; (2) primary percutaneous intervention as part of emergency care; (3) reporting of the MSI calculated as proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI in the first week after STEMI or alternatively reporting of the spatial extent of oedematous left ventricular myocardium on T2-weighted MRI along with the spatial extent of left ventricular necrotic myocardium on T1-weighted late gadolinium enhancement MRI, which enabled calculation of the MSI; (4) application of a unit compatible to the percentage of the whole left ventricular

myocardium for measuring oedema and necrosis on MRI (see online supplemental table 1); (5) reporting of CI, SD or IQR for the MSI or the spatial extents of myocardial oedema and necrosis on T2-weighted and T1-weighted late gadolinium enhancement MRI; (6) reporting of the time to reperfusion and (7) publication in English, German or French. Animal studies were excluded.

MEDLINE, EMBASE and ISI Web of Science were searched from inception until 16 May 2020. The search term for every database can be found in online supplemental file 1. Titles and abstracts of references found in the databases were screened before a full-text review was performed. The bibliography of included studies and reviews was screened for further eligible studies.

General information about the studies were extracted onto a predefined datasheet along with information on the time to reperfusion, MRI results, used MRI technique and basic patient characteristics.

The eligibility criteria and the search term were set up by two reviewers (BK and MD) and adjusted by discussion in the research group on non-invasive cardiovascular imaging at Charité—Universitätsmedizin Berlin. BK and HS performed the database search, title and abstract review, full-text review and data extraction independently; discrepancies were resolved by discussion, if necessary together with MD.

### Statistical analysis

If included studies did not state the MSI but the spatial extents of oedematous and necrotic myocardium measured by T2-weighted and T1-weighted late gadolinium enhanced MRI, we calculated the MSI ourselves as the proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI. The Delta Method was applied to estimate the variance and SD.<sup>22</sup>

To get an overview of the data, random effects models were applied to calculate pooled values for all extracted continuous variables: the MSI on T2-weighted and T1-weighted late gadolinium enhancement MRI, time to reperfusion, mean age and percent of male patients. The results of sub-groups within studies were included separately when available. We did not consider these observations to be independent from each other because of similar study methods. The intercept was thus allowed to vary randomly for each study to account for multiple observations per study. Each patient group's result was weighted by the inverse of its squared estimated SE. In case of the percent of male patients, the logit transformation was used to stabilise the variance and avoid a variance-on-mean relationship.<sup>23</sup> Furthermore, we calculated frequency distributions for all extracted categorical variables: T2-weighted MRI sequence, T1-weighted late gadolinium enhancement MRI sequence, T2-weighted MRI interpretation method, T1-weighted late gadolinium enhancement MRI interpretation method and timing of MRI. The individual categories for each categorical variable can be found in [table 1](#). Myocardial oedema appears

**Table 1** Basic characteristics of included study populations and MRI technique used by included studies

<b>Basic characteristics of included study populations</b>	
Characteristic	Pooled mean (95% CI)
Age, years	59.9 (95% CI: 59.0 to 60.7)
Male, % of patients	81.7 (95% CI: 79.3 to 83.9)
<b>MRI technique used by included studies</b>	
Technical parameter	% of included studies (n)
<b>Timing of MRI</b>	
3–7 days after STEMI	79% (30)
1–2 days after STEMI	21% (8)
<b>T2-weighted MRI sequence*</b>	
T2-weighted dark-blood TSE/FSE with IR (STIR)	90% (34)
T2-prepared bright-blood single-shot balanced SSFP	11% (4)
Hybrid TSE-SSFP (ACUTE)	5% (2)
BLADE k-space coverage for dark-blood TSE	3% (1)
<b>T1-weighted late gadolinium enhancement MRI sequence</b>	
PSIR using segmented FLASH readout (SPGR)	97% (37)
IR with single-shot SSFP	3% (1)
<b>T2-weighted MRI interpretation</b>	
Signal intensity >2 SD above remote myocardium	66% (25)
Manual contouring	29% (11)
FWHM algorithm	5% (2)
<b>T1-weighted late gadolinium enhancement MRI interpretation†</b>	
Signal intensity >5 SD above remote myocardium	37% (14)
Signal intensity >2 SD above remote myocardium	16% (6)
Signal intensity >3 SD above remote myocardium	3% (1)
Manual contouring	29% (11)
FWHM algorithm	11% (4)
Heiberg's method	8% (3)

\*One included study compared four T2-weighted MRI sequences.

†One included study applied two T1-weighted late gadolinium enhancement MRI interpretation methods.

ACUTE, acquisition for cardiac unified T2 oedema; FLASH, fast low angle shot; FSE, fast spin echo; FWHM, full width at half maximum; IR, inversion recovery; PSIR, phase-sensitive inversion recovery; SPGR, spoiled gradient echo; SSFP, steady-state free precession; STEMI, ST-segment elevation myocardial infarction; STIR, short-tau inversion recovery; TSE, turbo spin echo.

to be more stable in the time window between days 3 and 7 after STEMI,<sup>20</sup> and we thus categorised the timing of MRI into 1–2 days and 3–7 days after STEMI.

A mixed effects model was used to test for an association between the time to reperfusion and the MSI. The MSI was used as a dependent variable. The time to reperfusion was used as fixed effect. Again, the intercept was allowed to vary randomly for each study to account for multiple observations per study. Between-study heterogeneity was evaluated using Cochran's Q Test. We weighted each patient group's result by the inverse of the squared estimated SE of the mean of the MSI. On request of the reviewers, the model was also calculated after excluding outlying patient groups having a mean time to perfusion of less than 2 hours.

To explore the between-study heterogeneity in the mixed effects model, basic patient characteristics and MRI

parameters were included in the mixed effects model with the time to reperfusion as fixed effect and study as random effect. The mean age and gender distribution were included as continuous fixed effects, while the timing of MRI, T2-weighted MRI sequence, T1-weighted late gadolinium enhancement MRI sequence, T2-weighted MRI interpretation method and T1-weighted late gadolinium enhancement MRI interpretation method were included as categorical fixed effects. Each of the variables was included separately in the mixed effects model. The likelihood ratio test was applied to test whether the included variable provided a significantly better fit. All significant confounding variables were included together in the mixed effects model. Interactions were not included to avoid overfitting. The unexplained between-study variance  $\sigma^2$  was compared between the hereby resulting model and the original model without inclusion of confounding variables.

We assumed statistical significance for  $p$  values of less than 0.05. We used R (V.3.6.0, 2019, R Foundation of Statistical Computing) for the whole statistical analysis. The metafor R package was used to set up random and mixed effects models.<sup>24</sup> Two reviewers (PS and BK) planned the statistical analysis, which was performed afterwards by BK. The results were regularly discussed with and checked by PS to assure accuracy. The final results were discussed in the research group on non-invasive cardiovascular imaging at Charité—Universitätsmedizin Berlin.

### Risk of bias assessment

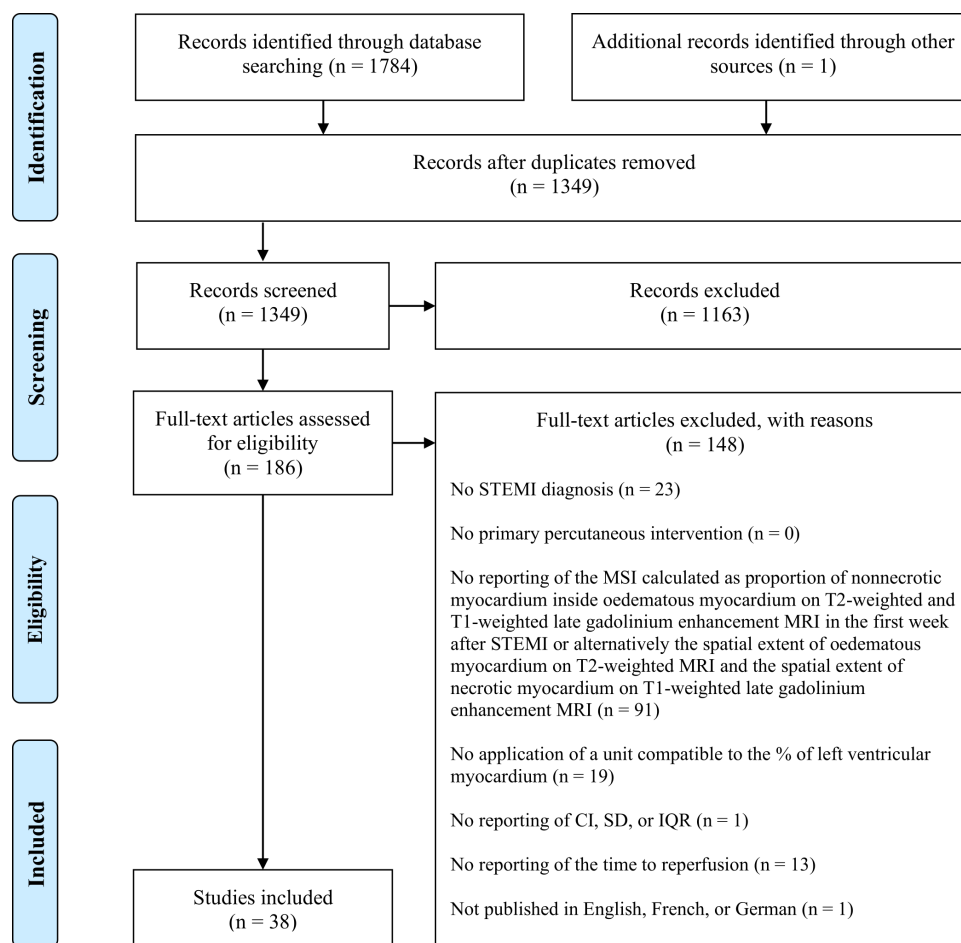
We applied the component approach<sup>25</sup> for assessing the risk of bias in individual studies, and thus developed a set of items for the domains of bias we considered most relevant to this meta-analysis: selection bias, attrition bias and detection bias. The items are explained in detail in online supplemental table 2. The risk of publication bias was assessed across studies by searching for obvious asymmetry in a funnel plot created with the data on the MSI. Begg and Mazumdar's correlation test<sup>26</sup> and Egger *et al*'s regression test<sup>27</sup> were applied as additional tests for publication bias.

### Patient and public involvement

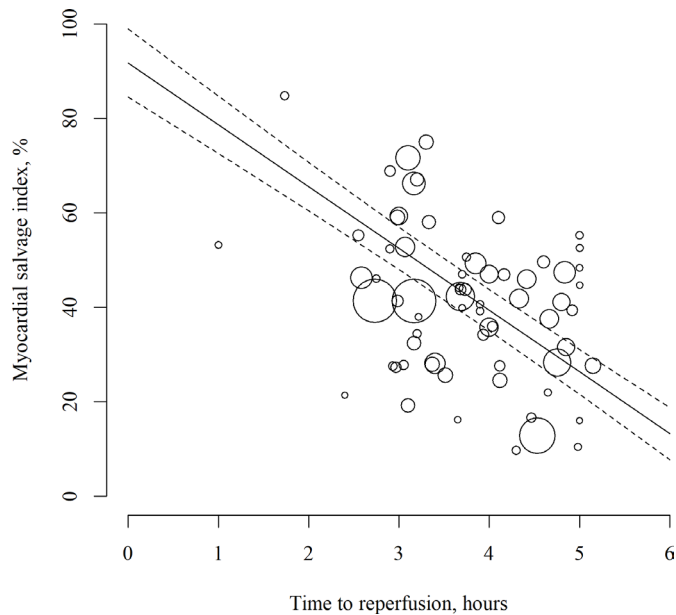
No patients were involved in setting the research question or design of the study. No patients were asked to advise on the interpretation of the results. We aim to present the results of the study to a wide audience, including patients, health professionals and members of the public.

### RESULTS

Study selection is summarised by the PRISMA flow chart in figure 1. We included 38 studies with 5106 patients in this meta-regression analysis.<sup>28–61</sup> Eighteen studies calculated and reported the MSI as proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI. For 19 studies, we calculated the MSI using available data on the spatial extent of oedematous and necrotic left ventricular myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI. Table 1 summarises basic patient characteristics and the used MRI technique.



**Figure 1** PRISMA flow chart; abstract and title review was performed of 1784 references that were found in MEDLINE, EMBASE and ISI Web of Science. We performed full-text review of 186 studies and included 38 studies in this meta-regression analysis. MSI, myocardial salvage index; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; STEMI, ST-segment elevation myocardial infarction; time to reperfusion, time from symptom onset until revascularisation.



**Figure 2** Inverse correlation between the time to reperfusion and the myocardial salvage index. The dashed lines represent the lower and upper 95% CI. The point size reflects the weight of a patient group, which was calculated as the inverse of the squared estimated SE. Time to reperfusion, time from symptom onset until revascularisation.

The pooled MSI was 42.6% (95% CI: 38.9 to 47.0). The pooled time to reperfusion was 3.8 (95% CI: 3.5 to 4.0). There was an inverse correlation between the time to reperfusion and the MSI (figure 2). Every hour of delay in reperfusion was associated with an absolute decrease of 13.1% (95% CI: 11.5 to 14.6;  $p < 0.001$ ) in the MSI. Between-study heterogeneity was considerable ( $\sigma^2 = 167.8$ ). Details of the mixed effects model can be found in table 2. The results of the mixed effects model calculated after excluding two outlying patient groups with a mean time to perfusion of less than 2 hours are summarised in online supplemental table 3.

Including basic patient characteristics and MRI parameters separately in the mixed effects model revealed that the inclusion of the timing of MRI ( $\chi^2(1) = 11.5$ ,  $p < 0.001$ ), T2-weighted MRI interpretation method ( $\chi^2(2) = 7.8$ ,  $p = 0.020$ ), T1-weighted late gadolinium enhancement MRI interpretation method ( $\chi^2(5) = 15.3$ ,  $p = 0.009$ ) and gender distribution ( $\chi^2(1) = 11.3$ ,  $p < 0.001$ ) resulted in a significantly better fit of the mixed effects model, while the inclusion of the T2-weighted MRI sequence ( $\chi^2(3) = 5.6$ ,  $p = 0.131$ ), T1-weighted late gadolinium enhancement MRI sequence ( $\chi^2(1) = 0.5$ ,  $p = 0.468$ ) and mean age ( $\chi^2(1) < 0.1$ ,  $p = 0.995$ ) did not. Inclusion of all significant confounding variables in the mixed effects model reduced the between-study heterogeneity by 45.2% to  $\sigma^2 = 91.9$ . The detailed parameters of this model can be found in online supplemental table 4.

The risk of selection bias, attrition bias and detection bias in included studies is summarised in figure 3. The detailed judgements for every study can be found in online supplemental tables 5–7. We neither find evidence

**Table 2** Model parameters of the mixed effects model

Model fit				
logLik	AIC	BIC		
-432.8	871.6	878.3		
Random effects				
Factor	$\sigma^2$	$\sigma$	Cochran's Q Test for heterogeneity	
			P value	
Study	167.8*	13.0*	<0.001	
Fixed effects				
Factor	Estimate	P value	Lower 95% CI	Upper 95% CI
(intercept)	91.7	<0.001	84.5	98.9
Time to reperfusion, hours	-13.1	<0.001	-14.6	-11.5

\*Exploration of heterogeneity: Separate inclusion of the timing of MRI ( $\chi^2(1) = 11.5$ ,  $p < 0.001$ ), T2-weighted MRI interpretation method ( $\chi^2(2) = 7.8$ ,  $p = 0.020$ ), T1-weighted late gadolinium enhancement MRI interpretation method ( $\chi^2(5) = 15.3$ ,  $p = 0.009$ ) and gender distribution ( $\chi^2(1) = 11.3$ ,  $p < 0.001$ ) resulted in a significantly better fit of the mixed effects model, while the inclusion of the T2-weighted MRI sequence ( $\chi^2(3) = 5.6$ ,  $p = 0.131$ ), T1-weighted late gadolinium enhancement MRI sequence ( $\chi^2(1) = 0.5$ ,  $p = 0.468$ ) and mean age ( $\chi^2(1) < 0.1$ ,  $p = 0.995$ ) did not. Inclusion of all significant confounding variables reduced the between-study heterogeneity by 45.2% to  $\sigma^2 = 91.9$  (see online supplemental table 4).

AIC, Akaike information criterion; BIC, Bayesian information criterion; logLik, log-likelihood.

of publication bias across studies by searching for obvious asymmetry in the created funnel plot with the data on the MSI measured by MRI (see online supplemental figure 1) nor by applying Begg and Mazumdar's rank correlation test ( $z = -1.4$ ,  $p = 0.173$ ) and Egger *et al*'s regression test ( $t = 0.7$ ,  $p = 0.507$ ).

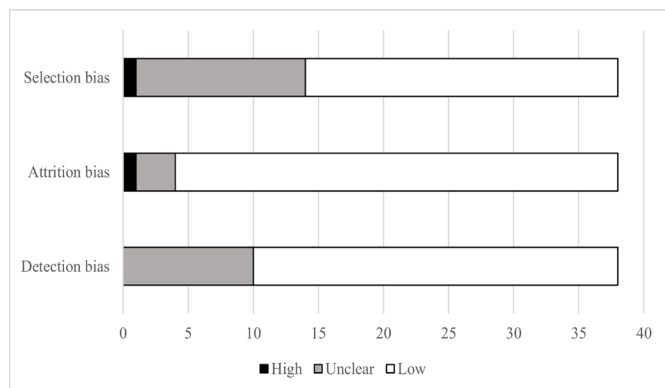
All raw data extracted from included studies can be found in online supplemental table 8.

## DISCUSSION

This meta-regression analysis was conducted to summarise existing data on the relation between the time to reperfusion and the MSI on T2-weighted and T1-weighted late gadolinium enhancement MRI after STEMI. The analysis showed that a short delay between symptom onset and revascularisation is associated with a large MSI, while a long delay between symptom onset and revascularisation is associated with a small MSI. There is considerable heterogeneity between studies.

### Comparison with other studies

We did not find a meta-analysis in MEDLINE, EMBASE, ISI Web of Science, Cochrane or PROSPERO that summarised data on the relation between the time to reperfusion and the MSI on T2-weighted and T1-weighted late gadolinium enhancement MRI after STEMI. While



**Figure 3** Risk of bias in individual studies. The risk of selection bias was judged as low in 25 of 34 studies, attrition bias in 34 studies and detection bias in 28 studies. In one study, the risk of selection bias was judged as high, and in another study, the risk of attrition bias.

most of, in this meta-regression analysis, included studies did not primarily study the impact of revascularisation delay on the MSI measured by T2-weighted and T1-weighted late gadolinium enhancement MRI, Francone *et al* subcategorised study patients into four time to reperfusion intervals.<sup>40</sup> Consistent with the main result of this meta-regression analysis, the data of Francone *et al* show an inverse correlation between the time to reperfusion and the MSI on T2-weighted and T1-weighted late gadolinium enhancement MRI.

As mentioned in the Introduction section, opinions differ on whether measurement of the extent of myocardial oedema by T2-weighted MRI allows delineation of the previously ischaemic area at risk differ.<sup>7–19</sup> In their landmark studies of the wavefront phenomenon of myocardial death, Reimer *et al* showed that necrotic myocardium gradually expands from the subendocardium toward the subepicardium in the ischaemic area at risk as long as ischemia persists, while this expansion can be halted by revascularisation of the ischaemic area.<sup>62 63</sup> The gradual expansion of myocardial necrosis measured by T1-weighted late gadolinium enhancement MRI within infarction-induced myocardial oedema measured by T2-weighted MRI with increasing time to reperfusion showed in this meta-analysis suggests a connection between the area at risk and the extent of myocardial oedema. However, the data cannot exclude underestimation or overestimation of the area at risk using myocardial oedema on T2-weighted MRI, and therefore the conclusion that myocardial oedema on T2-weighted MRI delineates the area at risk cannot be made.

### Meaning of the study and future perspective

Regardless of if myocardial oedema on T2-weighted MRI delineates the area at risk, underestimates or overestimates it, the gradual expansion of necrosis within infarction-induced oedema with increasing time to reperfusion indicates that measurement of the proportion of oedematous myocardium without necrosis by T2-weighted and T1-weighted late gadolinium enhancement MRI might

be of use for evaluating therapeutic efficiency, which may be helpful for studies investigating cardioprotective strategies.

The heterogeneity between studies suggests that other factors different from the time to reperfusion affect the proportion of oedematous myocardium without necrosis measured by T2-weighted and T1-weighted late gadolinium enhancement MRI after myocardial infarction. Since the heterogeneity analysis revealed significant confounding effects for the timing of imaging and image interpretation, differences in MRI methodologies should be resolved in the future to improve comparability of the results. The need for a standardisation of postmyocardial infarction MRI methodologies has also recently been highlighted by experts in the field.<sup>20</sup> The use of T2-mapping and T1-mapping MRI, which is a valuable and increasingly used alternative to conventional T2-weighted and T1-weighted late gadolinium enhancement MRI, may be a step forward in this regard since it allows a less subjective and more consistent delineation of oedematous and fibrotic myocardium.<sup>64</sup> The heterogeneity analysis furthermore suggests that gender differences should be considered when interpreting the MSI, which has previously been described as well.<sup>65 66</sup> Differences in cardioprotective strategies apart from the time to reperfusion may explain a fraction of the remaining heterogeneity.<sup>43 57</sup> Further research on the factors influencing the MSI measured by MRI is needed before a reliable evaluation of therapy efficiency may be possible by measuring the MSI with MRI.

### Strengths and limitations

This systematic review and meta-regression analysis has methodological strengths. Reporting followed the PRISMA guidelines.<sup>21</sup> After a comprehensive search in three electronic databases, a large number of studies could be included. State-of-the-art statistical tests for meta-regression analyses were applied for data analysis. We did not register a review protocol a priori, which increased the likelihood of our post hoc decisions to be biased.<sup>21</sup> Last, data on T2-mapping and T1-mapping MRI are not included in this meta-regression analysis. As mentioned above, mapping MRI may overcome inconsistencies when delineating the extent of myocardial oedema and fibrosis; however, only a few studies already applied mapping MRI for measuring the MSI. To have enough data for a conclusive meta-regression analysis, we therefore decided to search and include studies that used conventional T2-weighted and T1-weighted late gadolinium enhancement MRI.

### CONCLUSIONS

The MSI calculated as proportion of non-necrotic myocardium inside oedematous myocardium on T2-weighted and T1-weighted late gadolinium enhancement MRI after revascularisation in STEMI correlates inversely with the time to reperfusion, which indicates that cardioprotection

achieved by minimising the time to reperfusion leads to a higher MSI measured by MRI. The analysis revealed considerable heterogeneity between studies. A substantial part of the heterogeneity could be explained by differences in the gender distribution, timing and interpretation of MRI suggesting that the MRI-assessed MSI is not only influenced by cardioprotective therapy but also by patient characteristics and MRI parameters. One reviewer performed the database search, data extraction and statistical analysis, which limits the results.

**Contributors** Conceptualisation: BK and MD. Methodology: BK. Data curation: BK and HS. Formal analysis: BK and PS. Supervision: MD and PS. Visualisation: BK. Writing—original draft: BK. Writing—review and editing: MD. Guarantors: BK and MD.

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**Competing interests** MD and PS received financial support from the German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF) for the submitted work; outside the submitted work, MD received grants from the German Foundation of Heart Research, GE Healthcare, Bracco, Guerbet, Toshiba Medical Systems, Siemens Medical Solutions, Philips Medical Systems, German Research Foundation (DFG) and the European Union (funding programme FP7), and personal fees from German Research Foundation (DFG), Guerbet, Cardiac MR Academy Berlin, Bayer-Schering, Toshiba Medical Systems and Springer; outside the submitted work, PS received grants from the German Research Foundation (DFG), European Union and Bayer Pharma AG; no other relationships or activities that could appear to have influenced the submitted work.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplemental information.

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