Thermodilution-derived temperature recovery time: a novel predictor of microvascular reperfusion and prognosis after myocardial infarction

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Abstract

Background: Novel parameters that detect failed microvascular reperfusion might identify better the patients likely to benefit from adjunctive treatments during primary percutaneous coronary intervention (PCI).
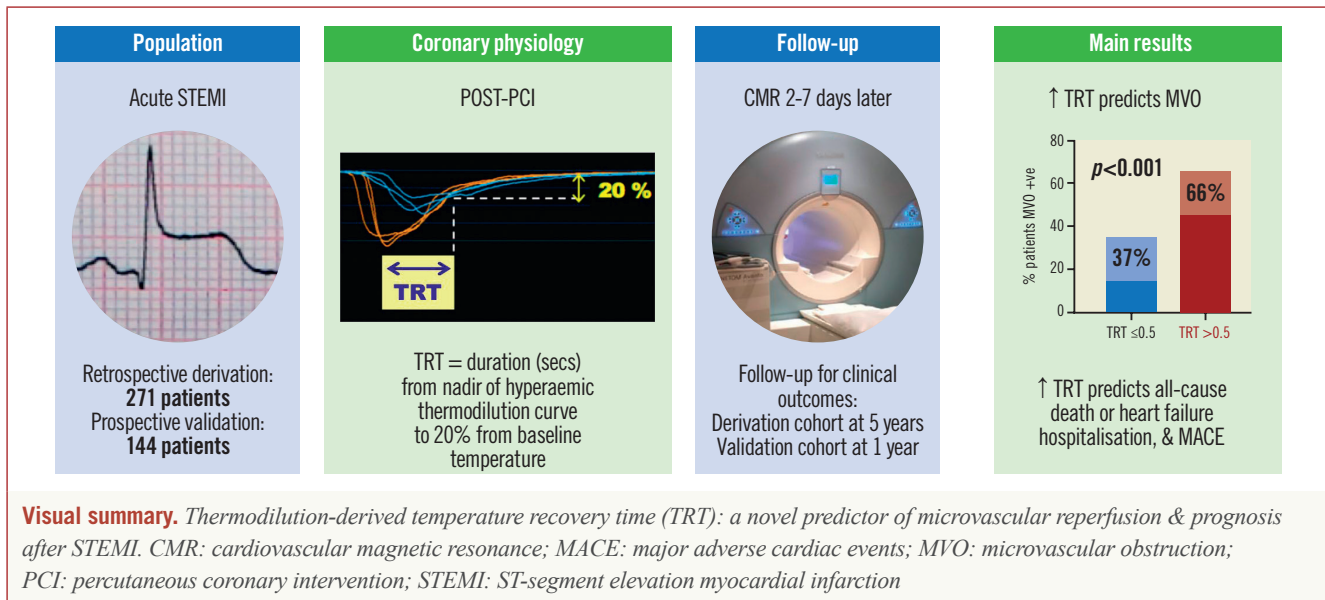
Aims: The aim of this study was to test the hypothesis that a novel invasive parameter, the thermodilution-derived temperature recovery time (TRT), would be associated with microvascular obstruction (MVO) and prognosis.

Methods: TRT was derived and validated in two independent ST-elevation myocardial infarction populations and was measured immediately post PCI. TRT was defined as the duration (seconds) from the nadir of the hyperaemic thermodilution curve to 20% from baseline body temperature. MVO extent (% left ventricular mass) was assessed by cardiovascular magnetic resonance imaging at 2-7 days.

Results: In the retrospective derivation cohort (n=271, mean age 60±12 years, 72% male), higher TRT was associated with more MVO (coefficient: 4.09 [95% CI: 2.70-5.48], p<0.001), independently of IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform, age and ischaemic time. At five years, higher TRT was multivariably associated with all-cause death/heart failure hospitalisation (OR 4.14 [95% CI: 2.08-8.25], p<0.001) and major adverse cardiac events (OR 4.05 [95% CI: 2.00-8.21], p<0.001). In the validation population (n=144, mean age 59±11 years, 80% male), the findings were confirmed prospectively.

Conclusions: TRT represents a novel diagnostic advance for predicting MVO and prognosis. ClinicalTrials.gov Identifiers: NCT02072850 & NCT02257294

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Visual summary. *Thermodilution-derived temperature recovery time (TRT): a novel predictor of microvascular reperfusion & prognosis after STEMI. CMR: cardiovascular magnetic resonance; MACE: major adverse cardiac events; MVO: microvascular obstruction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction*

Abbreviations

AUC	area under the curve
CFR	coronary flow reserve
CI	confidence interval
CMR	cardiovascular magnetic resonance
IMR	index of microcirculatory resistance
IQR	interquartile range
LV	left ventricular
OR	odds ratio
Pa	aortic pressure
PCI	percutaneous coronary intervention
Pd	distal coronary pressure
ROC	receiver operating characteristic
SD	standard deviation
STEMI	ST-segment elevation myocardial infarction
Tmn	mean transit time
TRT	temperature recovery time

Introduction

Microvascular obstruction (MVO) reflects failed myocardial reperfusion following acute ST-segment elevation myocardial infarction (STEMI). Despite routinely restoring epicardial coronary patency with primary percutaneous coronary intervention (PCI), MVO affects about half of patients and impairs prognosis[1]. There are no evidence-based treatments for MVO. Novel parameters that measure failed microvascular reperfusion accurately, and provide prognostic information incremental to clinical indices, have potential to refine clinical trial design. Stratified medicine is the identification of patient subgroups that are distinguishable from a heterogenous population by disease severity and potential response to treatments during primary PCI[2].

The index of microcirculatory resistance (IMR) is a validated measure of the immediate efficacy of microcirculatory reperfusion[3]. Higher IMR values indicate greater degrees of microvascular dysfunction. An IMR ≥32 or >40 predicts all-cause death or

heart failure hospitalisations[4]. An IMR >32 also predicts worse recovery of left ventricular (LV) function post STEMI[5] and is being used to select patients for clinical trials (RESTORE-MI [ACTRN12618000778280]). However, there are limitations for clinical translation, e.g., when calculating IMR the clinician should verify that the software has correctly positioned the distal coronary pressure (Pd) marker at the lowest stable Pd divided by mean aortic pressure (Pa) in hyperaemia (Pd/Pa)[2]. Second, manual saline injection can be a source of variability[2]. This variability can be reduced by thermodilution-based absolute flow and resistance measurement, using continuous saline infusion through a dedicated coronary catheter[6].

Coronary flow reserve (CFR)[7] and bimodal thermodilution waveforms[8] have also been associated with MVO and clinical outcomes. However, due to variations in resting flow, CFR has limited reproducibility[3]. The potential of bimodal waveform for clinical translation is limited by requiring off-line processing for waveform classification and, if used alone, bimodal waveform may miss some high-risk patients[2].

We theorised that the later part of the thermodilution curve might be less susceptible to variability in the speed of manual intracoronary saline injections. We conceived and evaluated a novel parameter, termed temperature recovery time (TRT). TRT is the time taken (seconds) for temperature recorded at the distal wire sensor to recover from the nadir value to baseline body temperature, during maximal hyperaemia. We hypothesised that TRT would be associated with the amount of MVO and clinical outcomes.

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Methods
POPULATION

TRT was derived from a retrospective cohort of 288 consecutive all-comer acute STEMI patients, who underwent emergency PCI, from a single centre (2011-2012) (MR-MI Study; NCT02072850)[9] **(Supplementary Figure 1)**.

Validation of TRT was performed prospectively in patients from the physiology substudy of the T-TIME trial (NCT02257294)[10]. From 2016 to 2017, 144 patients with acute STEMI, from three U.K. hospitals, were randomised to intracoronary alteplase (10 mg or 20 mg) or placebo, infused into the culprit artery before stenting. Eligibility criteria are shown in **Supplementary Appendix 1**.

The studies were approved by the National Research Ethics Service (13-WS-0119 and 10-S0703-28) and complied with the Declaration of Helsinki.

INVASIVE CORONARY PHYSIOLOGY

IMR (PdxTmn during hyperaemia[3]), CFR (resting Tmn ÷ hyperaemic Tmn[7]) and TRT were measured post PCI, using a pressure- and temperature-sensing guidewire (Abbott Vascular, Temecula, CA, USA), using standard thermodilution methodology **(Supplementary Appendix 2)**. The shapes of hyperaemic thermodilution curves were assessed as narrow unimodal, wide unimodal, or bimodal[8] **(Supplementary Appendix 2)**.

TRT was defined as the duration (seconds) from the nadir of the hyperaemic thermodilution curve to 20% from baseline temperature. The optimal threshold (20%) for the end of the TRT measurement was chosen after comparison of five percentage thresholds (i.e., 7.5%, 10%, 20%, 30% and 60%), from the first 100 consecutive patients in the derivation cohort. The percentage threshold that gave the highest area under the curve (AUC) for predicting MVO on receiver operating characteristic (ROC) curve analysis was used to define TRT **(Supplementary Figure 2)**. If the time when the temperature returns exactly to baseline is used, then the TRT parameter becomes sensitive to small errors in the measurement. The mean TRT (from triplicate measurements) was calculated using an automated algorithm using dedicated software (Coroventis, Uppsala, Sweden). In the derivation cohort, TRT was calculated retrospectively. In the validation cohort, coronary physiology parameters were calculated prospectively and were submitted to the data coordination centre prior to database lock.

ANGIOGRAM AND ELECTROCARDIOGRAM ANALYSES

Percentage ST-segment resolution on electrocardiograms (ECGs) obtained 60 minutes post reperfusion compared to pre reperfusion was calculated. Angiographic analyses included Thrombolysis In Myocardial Infarction (TIMI) coronary flow grade, corrected TIMI frame count and myocardial perfusion grade **(Supplementary Appendix 3)**.

CARDIOVASCULAR MAGNETIC RESONANCE

CMR imaging was performed at 1.5-Tesla. MVO extent (% LV mass) was demonstrated by late gadolinium enhancement imaging, at 2-7 days post PCI. The CMR protocols in these studies were similar and have been described previously[9,10].

CLINICAL OUTCOMES

The clinical outcomes were: (i) all-cause death or hospitalisation for heart failure after the initial acute STEMI, and (ii) major adverse cardiac events (MACE), defined as cardiac death, nonfatal MI, or heart failure hospitalisation. Clinical outcomes were independently assessed by physicians who were blinded to the other data. Clinical follow-up was completed for all patients.

STATISTICAL ANALYSIS

Associations with MVO extent were assessed with linear regression, and the regression coefficients represented mean change in MVO extent for a 1-unit increase in TRT. Association with MVO presence or clinical outcomes was evaluated using odds ratios (ORs), from logistic regression. The associations with MVO were adjusted for age, ischaemic time, CFR ≤2, IMR >32, hyperaemic Tmn >median and thermodilution waveform (bimodal or wide unimodal vs narrow unimodal). There was *a priori* concern that these covariates were clinically relevant confounders. ROC curve comparisons were made using the DeLong method. Further details of the statistical methods are shown in **Supplementary Appendix 4**.

Results

The flow of patients through the study is shown in **Supplementary Figure 1**. The findings were broadly similar when IMR >32 was substituted for IMR >40 in multivariable regression analyses **(Supplementary Table 1-Supplementary Table 3)**.

POPULATION CHARACTERISTICS
DERIVATION POPULATION

Seventeen patients were excluded from the derivation cohort because coronary physiology recordings were unsuitable for digital analysis. Among the 271 included patients (mean age 60±12 years, 72% male) **(Table 1, Table 2)**, most (92%) underwent primary PCI, whilst seven had PCI after successful thrombolysis, and 14 had PCI after failed thrombolysis.

TRT (median: 0.5; range: 0.1-2.5) had a right-skewed distribution **(Supplementary Figure 3)**. TRT correlated with IMR (r=0.8, p<0.001), CFR (r= -0.3, p<0.001) and with hyperaemic Tmn (r=0.9, p<0.001). Baseline and procedural characteristics associated with higher TRT in multivariable linear regression analysis were: IMR >32 (p<0.001), hyperaemic Tmn >median (p<0.001), CFR ≤2 (p<0.001), bimodal or wide unimodal thermodilution waveform (p=0.018), TIMI coronary flow grade post PCI ≤2 (p<0.001), and higher creatinine (p=0.044).

VALIDATION POPULATION

The median TRT in the validation population (n=144) was 0.5 (range: 0.2-2.4). Baseline and procedural characteristics **(Supplementary Table 4, Supplementary Table 5)** associated with higher TRT in multivariable linear regression analysis were bimodal or wide unimodal thermodilution waveform, higher final TIMI frame count and hyperaemic Tmn >median (all p<0.001).

ASSOCIATIONS OF TRT WITH MVO
DERIVATION POPULATION

In the derivation population, MVO presence/absence was available in 271 patients, and MVO extent was evaluable in 270 patients.

Table 1. Characteristics of the derivation population.

Derivation population characteristics		Overall (n=271)	TRT ≤0.5 (n=143)	TRT >0.5 (n=128)	p-value
Age, years		59.5±1.5	57.2±11.1	62.0±11.4	0.001[†]
Male		194 (71.6)	98 (68.5)	96 (75.0)	0.239[‡]
Current smoker		170 (62.7)	98 (68.5)	72 (56.3)	0.037[‡]
Body mass index, kg/m²		28.7±4.8	29.2±4.9	28.0±4.5	0.040[†]
Hypertension		85 (31.4)	45 (31.5)	40 (31.3)	0.969[‡]
Diabetes mellitus		30 (11.1)	15 (10.5)	15 (11.7)	0.747[‡]
Previous myocardial infarction		18 (6.6)	9 (6.3)	9 (7.0)	0.808[‡]
Reperfusion strategy	Primary PCI	250 (92.3)	134 (93.7)	116 (90.6)	0.344[‡]
	Thrombolysis followed by PCI	21 (7.8)	9 (6.3)	12 (9.4)	
Presenting heart rate, beats per minute		78.1±16.7	78.2±16.9	78.0±16.7	0.928[†]
Presenting systolic blood pressure, mmHg		135.2±25.1	134.5±24.8	133.2±25.4	0.217[†]
Ischaemic time, hours, median (IQR)		2.92 (2.0-5.4)	2.8 (2.0-5.0)	3.4 (2.2-5.7)	0.101[§]
Baseline creatinine, µmol/L		76.9±18.8	74.5±19.1	79.7±18.1	0.022[‡]
Procedural characteristics					
Culprit artery	Left anterior descending/ left main	100 (36.9)	50 (35.0)	50 (39.1)	0.364[‡]
	Circumflex	52 (19.2)	32 (22.4)	20 (15.6)	
	Right coronary artery	119 (43.9)	61 (42.7)	58 (45.3)	
No. of main vessels diseased	1	148 (54.6)	78 (54.6)	70 (54.7)	0.650[‡]
	2	84 (31.0)	42 (29.4)	42 (32.8)	
	3	39 (14.4)	23 (16.1)	16 (12.5)	
Thrombus aspiration		195 (72.0)	102 (71.3)	93 (72.7)	0.808[‡]
Glycoprotein IIb/IIIa inhibitor		249 (91.9)	132 (92.3)	117 (91.4)	0.786[‡]

Data are mean±SD, or n (%) unless otherwise stated. [†] Student's t-test. [‡] χ² test. [§] Mann-Whitney test. Missing data: ischaemic time, n=18; creatinine n=1. IQR: interquartile range; PCI: percutaneous coronary intervention; TRT: temperature recovery time

Table 2. From the derivation population, electrocardiogram, angiogram, and coronary physiology parameters on admission and CMR findings at 2-7 days after PCI for STEMI.

Derivation population parameters		Overall (n=271)	TRT ≤0.5 (n=143)	TRT >0.5 (n=128)	p-value
Electrocardiogram					
ST-segment resolution	Complete, ≥70%	123 (45.6)	76 (53.5)	47 (36.7)	0.020[‡]
	<70%	147 (54.4)	66 (46.5)	81 (63.3)	
Angiogram					
Initial TIMI coronary flow grade	0	157 (57.9)	73 (51.1)	84 (65.6)	0.029[‡]
	1	34 (12.6)	18 (12.6)	16 (12.5)	
	2	43 (15.9)	25 (17.5)	18 (14.1)	
	3	37 (13.7)	27 (18.9)	10 (7.8)	
Final TIMI coronary flow grade	1	1 (0.4)	1 (0.7)	0	0.003[‡]
	2	13 (4.8)	1 (0.7)	12 (9.4)	
	3	257 (94.8)	141 (98.6)	116 (90.6)	
TIMI frame count post PCI, median (IQR)		14.0 (10.0-24.0)	12.0 (8.2-20.0)	17.8 (10.6-25.4)	0.004[§]
Myocardial perfusion grade post PCI	≤1	76 (28.0)	32 (22.4)	44 (34.4)	0.028[‡]
	≥2	195 (72.0)	111 (77.6)	84 (65.6)	
Coronary physiology post PCI					
Hyperaemic Pa, mmHg, median (IQR)		76.0 (68.0-87.0)	76.0 (68.0-89.0)	76.0 (67.0-86.5)	0.515[§]
Hyperaemic Pd, mmHg, median (IQR)		70.0 (60.0-80.0)	69.0 (60.0-79.8)	71.0 (60.0-81.5)	0.983[§]
IMR, median (IQR)		24.0 (15.0-43.0)	15.4 (11.0-21.1)	44.1 (27.0-63.0)	<0.001[§]
IMR >32		100 (36.9)	13 (9.1)	87 (68.0)	<0.001[§]
CFR, median (IQR)		1.6 (1.1-2.1)	1.7 (1.3-2.4)	1.4 (1.0-1.8)	<0.001[§]
CFR ≤2		196 (72.3)	93 (66.0)	103 (83.1)	0.002[‡]
Hyperaemic Tmn, sec, median (IQR)		0.4 (0.2-0.6)	0.2 (0.2-0.3)	0.6 (0.4-0.9)	<0.001[§]
Hyperaemic Tmn >median		132 (48.7)	22 (15.4)	110 (0.9)	<0.001[‡]
Waveform	Bimodal	34 (12.5)	5 (3.5)	29 (22.7)	<0.001[‡]
	Wide unimodal	98 (36.2)	38 (26.6)	60 (46.9)	
	Narrow unimodal	139 (51.3)	100 (69.9)	39 (30.5)	
CMR 2-7 days after PCI					
Time from PCI to CMR, days		2.1±1.9	2.2±1.9	1.9±1.9	0.174[†]
MVO extent (% left ventricular mass)		0.2 (0.0-3.3)	0.0 (0.0-1.6)	2.0 (0.0-6.8)	<0.001[§]
MVO present		138 (50.9)	53 (37.1)	85 (66.4)	<0.001[‡]

Data are mean±SD, or n (%) unless otherwise stated. [‡] χ² test. [§] Mann-Whitney test. [†] Student's t-test. Missing: CFR, n=6; Pa post PCI, n=57; ST-segment resolution, n=1; MVO extent, n=1. CFR: coronary flow reserve; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; IQR: interquartile range; MVO: microvascular obstruction; Pa: aortic pressure; PCI: percutaneous coronary intervention; Pd: distal coronary pressure; TIMI: Thrombolysis In Myocardial Infarction; Tmn: mean transit time; TRT: temperature recovery time

MVO was present in 138 patients (51%). In ROC curve analysis, there was no difference in the discriminatory ability of TRT compared to IMR for predicting MVO presence **(Figure 1)**. The TRT cut-off with the highest combination of sensitivity (61%) and specificity (68%) for predicting MVO presence was >0.5. Case examples are shown in **Supplementary Figure 4**.

TRT dichotomised by 0.5 correctly predicted MVO presence, or absence, in 65% (n=175/271) of patients. IMR dichotomised by 32 correctly predicted MVO presence, or absence, in 62.0% (n=167/271) of patients. There was no difference in the predictive accuracy for detecting MVO presence/absence, when TRT and IMR dichotomised by 0.5 and 32, respectively, were compared, using the McNemar test (difference 2.95% [95% confidence interval [CI]: −2.39%, 8.29%], p=0.341). **Figure 2** shows discordance between IMR and TRT.

Continuous TRT was multivariably associated with MVO extent (coefficient: 4.09 [95% CI: 2.70-5.48], p<0.001), i.e., MVO extent increased by 4.09 units for every 1-unit increase in TRT. Continuous TRT was also multivariably associated with MVO presence (OR 5.26 [95% CI: 2.52-11.74], p<0.001). The performance of TRT >0.5 for predicting MVO is shown in **Table 3**.

VALIDATION POPULATION

In the validation population, continuous TRT was multivariably associated with MVO extent (coefficient: 2.86 [95% CI: 1.26-4.46], p=0.001).
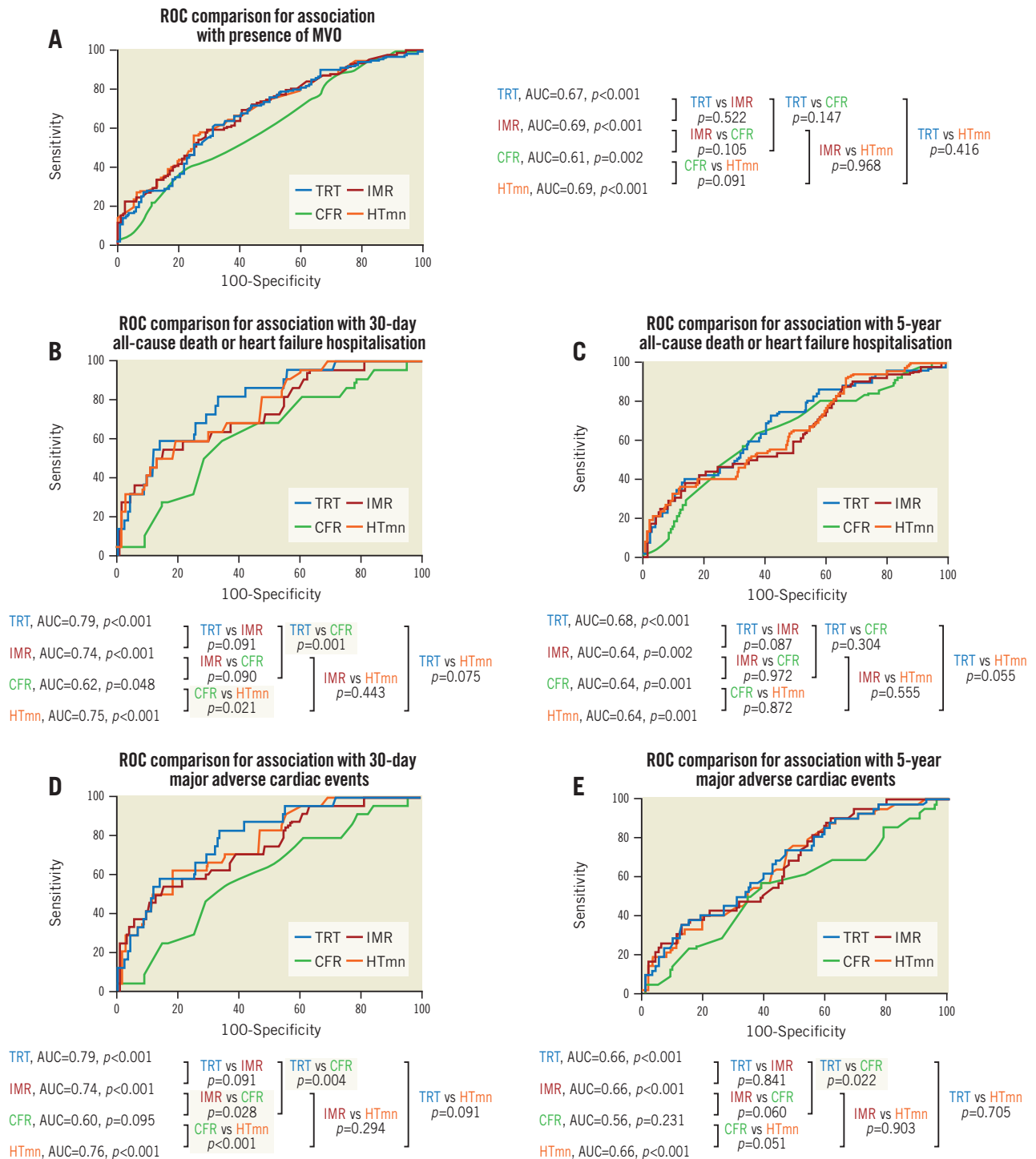
Figure 1. *ROC curves from the derivation population, for association with presence of MVO (A), death/heart failure hospitalisation (B & C), and MACE (D & E). CFR: coronary flow reserve; HTmn: mean hyperaemic transit time; IMR: index of microcirculatory resistance; MVO: microvascular obstruction; ROC: receiver operating characteristic; TRT: temperature recovery time*

PROGNOSTIC SIGNIFICANCE OF TRT

DERIVATION POPULATION

During the initial 30 days post STEMI, all-cause death/heart failure hospitalisation occurred in 22 patients (8%), and MACE occurred in 24 patients (9%). ROC analysis showed that TRT had superior discriminatory ability compared to CFR for predicting 30-day

clinical outcomes **(Figure 1)**. TRT was multivariably associated with 30-day clinical outcomes, independent of IMR **(Table 3)**.

During a median follow-up of five years, 52 patients died or experienced heart failure hospitalisation, and 43 patients experienced MACE. ROC curve analysis demonstrated that TRT had superior discriminatory ability compared to CFR for predicting
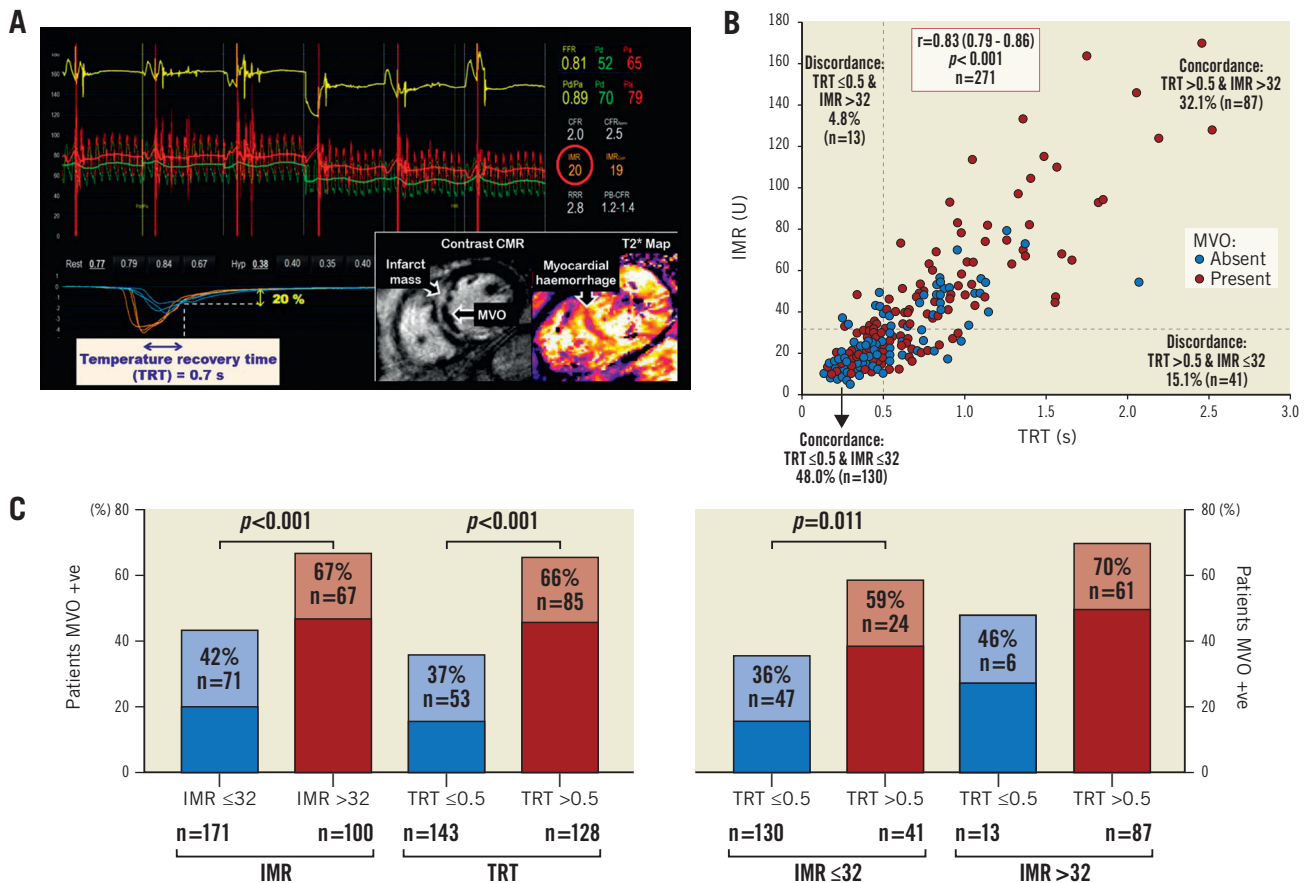
Figure 2. *From the derivation population, example of IMR-TRT discordance (A*), scatter graph showing IMR-TRT discordance and IMR/ TRT–MVO (microvascular obstruction) discordance (B), and patients with MVO stratified by combinations of IMR ≤32, IMR >32, TRT ≤0.5 and TRT >0.5 (C**). * Thermodilution curves obtained in triplicate at rest (blue) and during hyperaemia (orange), after primary percutaneous coronary intervention. This patient had high TRT and normal IMR. CMR imaging revealed transmural anteroseptal myocardial infarction complicated by MVO. ** p-values from chi-square test (χ^2). CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; TRT: temperature recovery time*

five-year MACE **(Figure 1)**. TRT was multivariably associated with five-year clinical outcomes **(Table 3)**.

VALIDATION POPULATION

During one-year follow-up in the validation population, all-cause death/heart failure hospitalisation occurred in 22 patients (15%), and MACE occurred in 23 patients (16%). Continuous TRT was multivariably associated with all-cause death/heart failure hospitalisations (OR 6.10 [95% CI: 2.42-15.42], p<0.001), and MACE (OR 7.65 [95% CI: 1.87-31.29], p=0.005), independent of IMR >32, CFR ≤2, hyperaemic Tmn >median and thermodilution waveform. The results were similar when IMR >32 was substituted for IMR >40 in the multivariable model (all-cause death/heart failure hospitalisation: OR 5.85 [95% CI: 1.43-23.94], p=0.014, and MACE: OR 5.84 [95% CI: 1.44-23.76], p=0.014).

REPEATABILITY OF TRT AND ASSOCIATIONS WITH HAEMODYNAMICS

Paired TRT measurements, obtained 0.5-8 minutes apart, post primary PCI, by four cardiologists in 13 patients were correlated (r=0.93, p<0.001), with a mean difference between duplicate TRT measurements of 0.02±0.08 (p=0.489). The coefficient of variation from duplicate TRT measurements was 12.7%. The Bland-Altman plot is shown in **Supplementary Figure 5**. The coefficient of variation from duplicate IMR measurements was 15.5%.

Relationships between TRT, IMR, CFR, or hyperaemic Tmn with haemodynamic parameters were examined in the derivation cohort, because predictive performance may be impaired if influenced by haemodynamic conditions. Pd did not correlate with TRT (r= –0.04, p=0.543), or hyperaemic Tmn (r= –0.01, p=0.883). However, Pd was correlated with IMR (r=0.3, p<0.001) and CFR (r=0.2, p=0.014). Pa did not correlate with TRT (r= –0.1, p=0.311), or hyperaemic Tmn (r= –0.05, p=0.506). However, Pa was correlated with IMR (r=0.2, p=0.001) and CFR (r=0.2, p=0.011).

Neither TRT, IMR, nor hyperaemic Tmn was correlated with heart rate, but CFR was (TRT, r= –0.1, p=0.399; IMR, r=0.01, p=0.926; hyperaemic Tmn, r= –0.03, p=0.615; CFR, r= –0.13, p=0.030).

Discussion

We have described and validated a novel measure for the efficacy of microvascular reperfusion in two independent STEMI cohorts.

Table 3. From the derivation population, logistic and linear regression analyses, showing associations between TRT, MVO, and clinical outcomes.

	Univariable analysis		Multivariable analysis	
	OR/coefficient (95% CI)	*p*-value	OR/coefficient (95% CI)	*p*-value
Associations with MVO extent (%LV mass) on CMR 2-7 days post PCI*				
TRT continuous	4.38 (3.07-5.68)	<0.001	4.09 (2.70-5.48)	<0.001
TRT >0.5	2.84 (1.71-3.97)	<0.001	2.69 (1.49-3.89)	<0.001
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			1.53 (-0.18, 3.23)	0.080
Associations with MVO presence on CMR 2-7 days post PCI*				
TRT continuous	5.52 (2.59-11.77)	<0.001	5.26 (2.52-11.74)	<0.001
TRT >0.5	3.36 (2.04-5.53)	<0.001	3.01 (1.75-5.16)	<0.001
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			1.72 (0.78-3.77)	0.178
Associations with 30-day death/heart failure hospitalisation‡				
TRT continuous	6.64 (2.90-15.24)	<0.001	7.37 (2.37-22.94)	0.001
TRT >0.5	8.14 (2.35-28.20)	0.001	7.13 (1.78-28.66)	0.006
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			4.48 (1.14-17.63)	0.032
Associations with death/heart failure hospitalisation at median 5 years§				
TRT continuous	3.85 (1.97-7.51)	<0.001	4.14 (2.08-8.25)	<0.001
TRT >0.5	3.11 (1.63-5.93)	0.001	6.44 (2.48-16.71)	<0.001
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			5.37 (2.00-14.43)	0.001
Associations with 30-day MACE‡				
TRT continuous	6.51 (2.89-14.69)	<0.001	7.38 (2.41-22.55)	<0.001
TRT >0.5	9.16 (2.66-31.51)	<0.001	8.57 (2.18-33.63)	0.002
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			5.18 (1.34-19.99)	0.017
Associations with MACE at median 5 years§				
TRT continuous	3.55 (1.79-7.03)	<0.001	4.05 (2.00-8.21)	<0.001
TRT >0.5	2.39 (1.21-4.71)	0.012	2.65 (1.32-5.30)	0.006
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			2.19 (0.76-6.29)	0.145

*Other variables in multivariable model: age, ischaemic time, IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform. ‡Other variables in multivariable model: IMR >32. §Other variables in multivariable model: IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform. CFR: coronary flow reserve; CI: confidence interval; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; LV: left ventricular; MVO: microvascular obstruction; OR: odds ratio; PCI: percutaneous coronary intervention; Tmn: mean transit time; TRT: temperature recovery time

Higher TRT had clinical utility for predicting MVO extent and clinical outcomes, independent of established predictors. The results support the potential clinical utility of TRT for stratified medicine in patients with acute MI.

Though TRT and IMR are correlated, we observed discordance between high and low dichotomised TRT and IMR values in 54 patients (20%), indicating that these parameters are not one and the same. We used 32 as the cut-off for dichotomising IMR, because IMR >32 is being used to select patients for inclusion in clinical trials[2]. When an IMR cut-off of 40 was used, discordance between high and low dichotomised IMR and TRT occurred in 61 patients (23%). TRT measures different aspects of the thermodilution curve than Tmn, which is used to calculate IMR. For calculating IMR, the Tmn starts at the steepest downslope of the temperature-time curve (measured by the wire's shaft thermistor). This transit time measurement ends midway between the peak temperature drop (measured by the wire's distal thermistor) and 10% from return of the distal thermistor temperature to baseline. In contrast, the TRT measurement only incorporates the part of the temperature-time curve from peak temperature drop to 20% from return to baseline temperature. The independence of TRT, but not IMR, from coronary and systemic haemodynamics (i.e., Pa or Pd) further distinguishes TRT from IMR.

The reproducibility of IMR may be influenced by coronary perfusion pressure and variability in manual bolus injection speed[2]. It is theoretically plausible that, when injection speed is slower, it would take longer for the initial part of the thermodilution curve to reach peak temperature drop than when injection speed is faster. It is potentially plausible that the recovery part of the thermodilution curve (nadir to baseline body temperature) may be less sensitive to this variability. Published literature evaluating this theory is not available, hence it may merit evaluation in future research.

Considering translation to clinical practice, measuring TRT should be more straightforward for use by clinicians who are less experienced with thermodilution methodology. This is because TRT is calculated precisely using an automated algorithm using dedicated software in the catheterisation laboratory. Alternatively, for precise calculation of IMR, the operator must confirm that the position of the marker is at the lowest stable Pd/Pa during hyperaemia, which may be positioned incorrectly by automated software. The classification of bimodal thermodilution waveforms is not automatically determined by analysis software. CFR, which reflects epicardial and microcirculatory vasodilator capacity, and residual epicardial stenosis, is calculated using an automated algorithm; however, CFR does not improve the predictive ability of IMR alone[9].

Reliable identification of patients with a high probability of having MVO may potentially improve research study design by selecting patients in the catheterisation laboratory for inclusion in therapeutic trials. Moreover, accurate identification of STEMI patients who will not develop MVO could potentially reduce healthcare costs through stratification and triage for earlier hospital discharge[11].

Strengths and limitations

Strengths of this study include the blinding of coronary physiology measurements to minimise bias, the high follow-up rates with CMR, and the prospective validation of TRT with independent adjudication of clinical events.

A limitation is that duplicate TRT and IMR measurements were available in only 13 patients. Therefore, further research is needed to study the reproducibility of TRT compared to IMR in a larger number of patients. Second, the limited number of composite outcome events constrained the statistical power of the multivariable models.

Limitations of the bolus-derived thermodilution technique should be considered. Notably, higher intra-observer variability of thermodilution-derived, compared to Doppler-derived CFR measurements has been demonstrated[12], the hyperaemic response to adenosine can be attenuated by caffeine, and manual bolus injections of saline can be a source of variability. Thermodilution-based absolute flow and microvascular resistance measurements, using continuous infusion of saline to induce steady-state maximal hyperaemia, has potential to have superior reproducibility[6]. However, it requires a dedicated infusion catheter and can be more technically challenging.

A test with a binary cut-off (normal/abnormal) is generally helpful for patient stratification in the clinic and in therapeutic trials. However, the optimal cut-off for predicting adverse events may vary between different populations and different endpoints. There was discordance between post-PCI TRT (dichotomised by 0.5) and MVO presence/absence in about one third of patients, which was also observed when an IMR threshold of 32 was applied. There may be several explanations. First, higher TRT and IMR are correlated with greater amounts of MVO, hence one would expect there to be discordance when binary cut-offs are applied. Second, the

differences in timing of measuring TRT or IMR (acute) versus CMR imaging (subacute) are relevant because microvascular dysfunction is dynamic within minutes to the first few days after reperfusion. When microvascular function is measured immediately post primary PCI, reversible oedema may contribute more to microvascular injury than on CMR 2-7 days later, where irreversible microvascular injury (including myocardial haemorrhage) may persist.

A more robust way to validate TRT could be a comparison with positron emission tomography, or an experimental model with perivascular flow probes or microspheres, enabling calculation of coronary flow and myocardial resistance. Further research is warranted to validate the findings reported in this paper.

Conclusions

TRT predicts MVO and prognosis, independent of established predictors. TRT represents a novel diagnostic advance for detecting failed microvascular reperfusion invasively. TRT has potential to refine risk stratification after primary PCI. Further research is needed to evaluate the potential clinical utility of TRT-guided selection of patients for adjunctive treatments during primary PCI.

Impact on daily practice

IMR is a validated invasive coronary physiology test for evaluating the immediate efficacy of microcirculatory reperfusion; however, it has some limitations for clinical translation. We describe and validate a novel physiology parameter, the thermodilution-derived temperature recovery time (TRT), which predicts MVO and prognosis, independent of IMR >32 and other established predictors. TRT is a novel diagnostic advance for detecting failed microcirculatory reperfusion, which has potential to refine risk stratification and selection of patients for adjunctive treatments after primary PCI.

Conflict of interest statement

C. Berry is supported by a BHF Centre of Research Excellence award (RE/18/6134217; FS/16/74/32573) and grant 12/170/4 from the NIHR-EME. C. Berry is named on institutional research and/or consultancy agreements between Glasgow University and Abbott

Vascular, AstraZeneca, Boehringer Ingelheim, Coroventis, Corstem, GSK, HeartFlow, Novartis, Philips, and Siemens Healthcare. These companies had no involvement in the manuscript. K.G. Oldroyd has served as a consultant and speaker for Abbott Vascular and Boston Scientific. A. Maznyczka reports grants and non-financial support from the British Heart Foundation during the conduct of the study. The other authors have no conflicts of interest to declare.

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Supplementary data

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Supplementary Table 3. Summary of logistic and linear regression analyses, showing univariable and multivariable associations (with IMR >40 in multivariable models) between TRT and angiogram parameters at the end of PCI.

Supplementary Table 4. Characteristics of the validation population.

Supplementary Table 5. From the validation population, electrocardiogram, angiogram, and coronary physiology parameters on admission and CMR findings at 2-7 days after PCI for STEMI.

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-19-00904

Supplementary data

Supplementary Appendix 1. Eligibility criteria for the T-TIME clinical trial

Patients with a clinical diagnosis of acute ST-segment elevation myocardial infarction (STEMI) were eligible for randomisation according to the following eligibility criteria:

Inclusion

- Acute MI (symptom onset ≤6 hours) with persistent ST-segment elevation or recent left bundle branch block.
- Coronary artery occlusion (Thrombolysis In Myocardial Infarction [TIMI] coronary flow grade 0 or 1), or impaired coronary flow (TIMI coronary flow grade 2, slow but complete filling) in the presence of definite angiographic evidence of thrombus (TIMI grade 2 or more).
- Proximal-mid culprit lesion location in a major coronary artery (i.e., the right, left anterior descending, intermediate, or circumflex artery).
- Radial artery access.
- TIMI coronary flow grade ≥2 pre-stent achieved prior to randomisation.
- Informed consent, i.e., only patients who were sufficiently well to understand the information about the study, as described by the attending cardiologist, were eligible to participate.

Exclusion

- Normal flow in the culprit coronary artery at initial angiography (TIMI grade 3).
- Functional coronary collateral supply (Rentrop grade 2/3) to the culprit artery.
- Previous infarction in the culprit artery (known or suspected clinically, e.g., wall motion abnormality revealed by echocardiography).
- Cardiogenic shock (Killip Class IV).
- Multivessel percutaneous coronary intervention (PCI) intended before the day 2-7 cardiovascular magnetic resonance (CMR) scan.
- Estimated body weight <60 kg.
- Non-cardiac comorbidity with expected survival <1 year.
- Contraindication to contrast-enhanced CMR imaging.
- Pacemaker, or implantable defibrillator.
- Known impaired renal function (estimated glomerular filtration rate <30 ml/min).
- Significant bleeding disorder either at present or within the past six months.
- Known haemorrhagic diathesis.
- Patient with current concomitant oral anticoagulation therapy (international normalised ratio >1.3), including apixaban, dabigatran and rivaroxaban.
- Any history of central nervous system damage (i.e., neoplasm, aneurysm, intracranial or spinal surgery).

- Severe hypertension (blood pressure >180/110 mmHg) not controlled by medical therapy.
- Major surgery, biopsy of a parenchymal organ, or significant trauma within the past three months (this includes any trauma associated with the current acute MI).
- Recent trauma to the head (<2 months).
- Prolonged cardiopulmonary resuscitation (>2 minutes) within the past two weeks.
- Acute pericarditis and/or subacute bacterial endocarditis.
- Acute pancreatitis.
- Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis.
- Active peptic ulceration.
- Arterial aneurysm and known arterial/venous malformation.
- Neoplasm with increased bleeding risk.
- Any known history of haemorrhagic stroke, or stroke of unknown origin.
- Known history of ischaemic stroke, or transient ischaemic attack in the preceding six months.
- Dementia.
- Hypersensitivity to gentamicin, or natural rubber.
- Incapacity, or inability to provide informed consent.
- Previous randomisation to this study, or participation in a study with an investigational drug, or medical device within 90 days prior to randomisation.
- Women of child-bearing potential (i.e., pre-menopausal), or breast feeding.
- Requirement for immunosuppressive therapy at any time during the preceding three months. This would include corticosteroids (but not inhaled or topical), drugs used following transplantation (e.g., tacrolimus, cyclosporine), anti-metabolite therapies (e.g., mycophenolic acid, azathioprine, leflunomide and immunomodulators including biologics (e.g., adalimumab, or etanercept) and disease-modifying anti-rheumatic drugs. This list is not exhaustive.
- Active or prophylactic treatment with oral, or parenteral antibiotic, antifungal, or antiviral therapy, to prevent or treat infection.
- Any anti-cancer treatment (excluding surgery as this is covered above) at any time during the preceding three months, including chemotherapy, radiotherapy, and treatment with biologics, such as vascular endothelial growth factor receptor (VEGFR) inhibitors (e.g., bevacizumab, pazopanib). This list is not exhaustive.
- Any significant concurrent, or recent condition(s) not listed above that in the opinion of the treating clinician would pose an additional risk to the patient.

Supplementary Appendix 2. Invasive coronary physiology acquisition and analysis methods

Intracoronary nitroglycerine (200 µg) was administered to the culprit artery. A calibrated wire was equalised to guide catheter pressure, then advanced to the distal third of the culprit artery. Using thermodilution, the mean transit time (Tmn) of a hand-injected 3 ml bolus of room temperature saline was measured in triplicate at rest and during steady-state maximal hyperaemia, induced by intravenous adenosine (140 µg/kg/min). Simultaneous measurements of Pa and Pd were made.

To mitigate potential bias through disclosure of IMR, CFR, or TRT results, the operators were blinded by obscuring the display of the RadiAnalyzer™ Xpress monitor (Abbott Vascular, Santa Clara, CA, USA). Experienced physiology technicians recorded the thermodilution data and quality assured the acquisition. Data were extracted from the RadiAnalyzer Xpress instrument and analysed offline (Coroventis Research AB, Uppsala, Sweden). At the end of primary PCI when IMR was measured after stenting, there was no residual epicardial stenosis, therefore IMR correction with wedge pressure or Yong's formula was not required.

A narrow unimodal waveform was defined as an acute temperature reduction (duration of <0.42 seconds from the beginning of the temperature reduction to nadir temperature) followed by rapid return to resting temperature. A wide unimodal waveform was defined as a temperature decrease to nadir >0.42 seconds, followed by a gradual return to baseline temperature. A bimodal waveform was defined as having two distinct nadirs, with a valley deeper than 20% of peak temperature drop.

The coronary physiology data were evaluated in the Glasgow Core Laboratory, according to a standard operating procedure, by an investigator blinded to the CMR data (A.M. Maznyczka) with the readings second read by an experienced investigator (C. Berry). The final coronary physiology data were established by consensus agreement.

Supplementary Appendix 3. Angiogram acquisition and analysis methods

Coronary angiograms were acquired during emergency care with cardiac catheter laboratory X-ray and information technology equipment. The angiograms were analysed using post-processing software (QAngio® XA; Medis, Leiden, the Netherlands) by experienced investigators who were blinded to treatment allocation. Catheter calibration was performed using the catheter calibration function on Medis QAngio. For each lesion, a view perpendicular to the long axis of the vessel was used in order to avoid foreshortening and overlap of branches. The single plane projection showing the best opacified and most severe lesion with minimal foreshortening and minimal branch overlap was selected. Feedback was provided to sites on the quality and completeness of the angiograms.

Non-culprit lesions ≥50% visual stenosis, in main vessels, were included in assessment for multivessel disease.

TIMI coronary flow grade

The TIMI coronary flow grade was assessed using the following definitions:

TIMI coronary flow grade	Definition
0	No flow
1	Minimal flow past obstruction
2	Slow (but complete) filling and slow clearance
3	Normal flow and clearance

TIMI myocardial perfusion grade

TIMI myocardial perfusion grade provides a score for ground-glass appearance ("blush") of the contrast entering the microvasculature and contrast washout. TIMI myocardial perfusion grade was assessed according to the following definitions:

TIMI myocardial perfusion grade	Definition
0	Minimal or no myocardial blush in the distribution of the culprit artery.
1	Myocardial blush is present in the distribution of the culprit artery, but there is incomplete clearance of dye between injections (with ~30 seconds between injections).
2	Myocardial blush is present in the distribution of the culprit artery, but there is slow contrast entry into the microvasculature and slow clearance of contrast. Specifically, blush is strongly persistent (i.e., either does not or only minimally diminishes in intensity) beyond three cardiac cycles after injection.
3	Myocardial blush is present in the distribution of the culprit artery, with normal entry and exit of dye (mild/moderate persistence of dye beyond three cardiac cycles, but notably reduced after three cardiac cycles). Blush that is only mild intensity throughout three cardiac cycles after injection (washout phase) but fades minimally is also classified as grade 3.

TIMI frame count

The TIMI frame count represents the amount of time (in frames) for contrast dye to reach a standardised distal landmark. If the culprit vessel was the left anterior descending artery the frame count was divided by 1.7 (correcting for longer vessel length).

Supplementary Appendix 4. Statistical methods

Between-group comparisons of continuous variables used the Student's t-test or Mann-Whitney test. Differences in proportions were assessed with a χ^2 test. Associations with MVO extent were assessed with linear regression, and the regression coefficients represented mean change in MVO extent for a 1-unit increase in TRT. Association with MVO presence or clinical outcomes was evaluated using odds ratios (ORs), from logistic regression. A preponderance of heart failure episodes occurred during the index hospitalisation, therefore the assumption for the Cox proportional hazards regression model for constant effects over time was not met. The associations with MVO were adjusted for the following covariates: age, ischaemic time, CFR ≤2, IMR >32, hyperaemic Tmn >median and thermodilution waveform (bimodal or wide unimodal vs narrow unimodal). There was a priori concern that these covariates were clinically relevant confounders. Non-dichotomised continuous TRT, IMR, CFR, or hyperaemic Tmn were not included together in multivariable models due to collinearity. Stepwise regression was performed, and the validity of regressions was verified by analysis of model residuals, testing for heteroscedasticity and multicollinearity.

The predictive value of TRT was evaluated using the McNemar test. Receiver operating characteristic (ROC) curve analysis was performed to detect the optimal cut-off values for predicting MVO. In this, sensitivity and specificity were considered equally important, therefore the optimal cut-off was considered as the one giving the maximum Youden index. ROC comparisons were made using the DeLong method.

All tests were two-tailed and a p-value of <0.05 was considered statistically significant. There was no imputation for missing values. Statistical analyses were performed in SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA), or MedCalc Statistical Software version 18 (MedCalc Software, Ostend, Belgium).
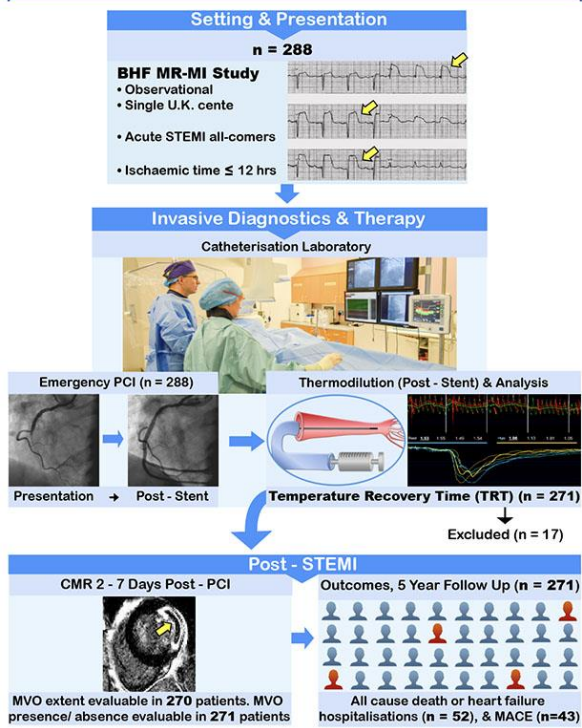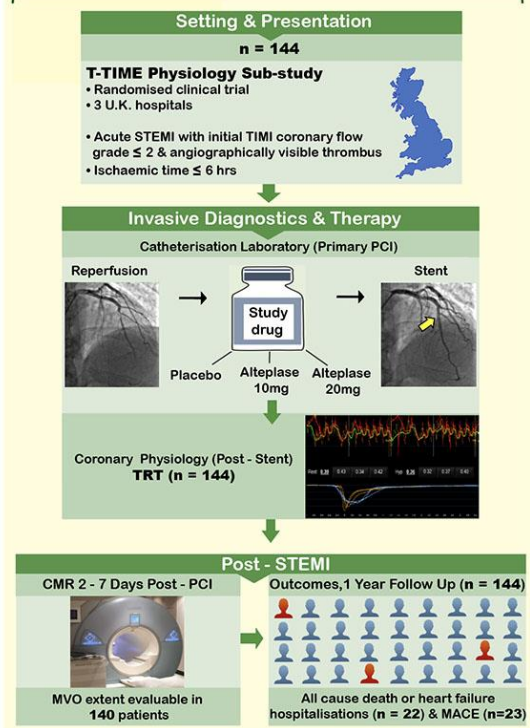
Supplementary Figure 1. Study design and patients included for retrospective derivation and prospective validation of TRT (temperature recovery time).

BHF: British Heart Foundation; CMR: cardiovascular magnetic resonance imaging; PCI: percutaneous coronary interventions; STEMI: ST-segment elevation myocardial infarction; T-TIME: Trial of low-dose adjunctive alTeplase during primary PCI
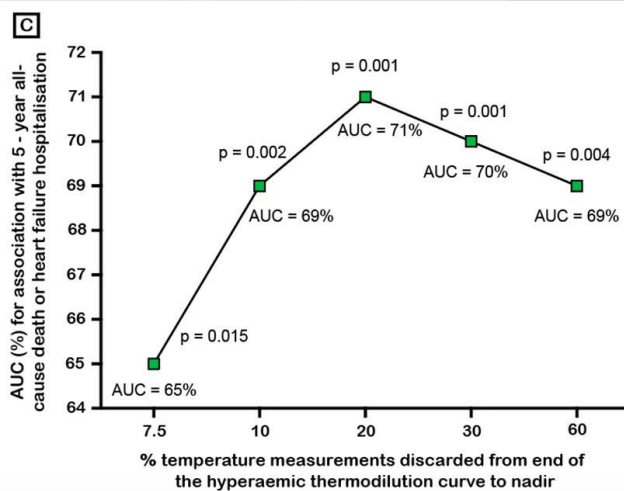
Supplementary Figure 2. Derivation of the optimal definition for TRT (temperature recovery time).

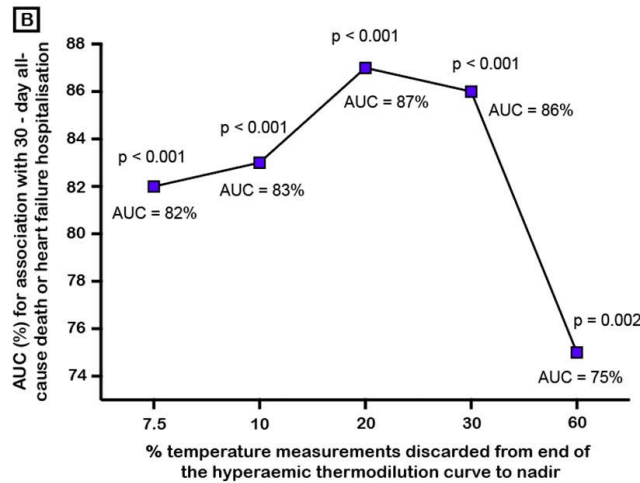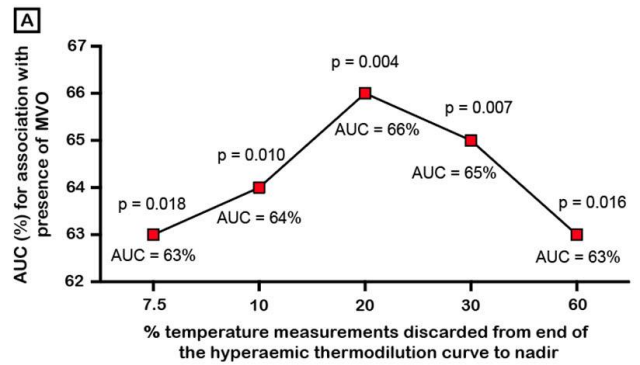Data from the first 100 consecutive patients in the derivation cohort. Area under the curves (AUCs) from receiver operating characteristic curve analyses, for predicting: (A) microvascular obstruction (MVO) presence/absence, (B) 30-day all-cause death/heart failure hospitalisation, and (C) five-year all-cause death/heart failure hospitalisation. Five different thresholds from the end of the thermodilution curve (i.e., 7.5%, 10%, 20%, 30% and 60%) were used to calculate durations of the thermodilution recovery curve (in seconds) from nadir temperature. The dots represent AUCs. The mean was calculated from three hyperaemic thermodilution curves for each percentage threshold (i.e., 7.5%, 10%, 20%, 30% and 60%).
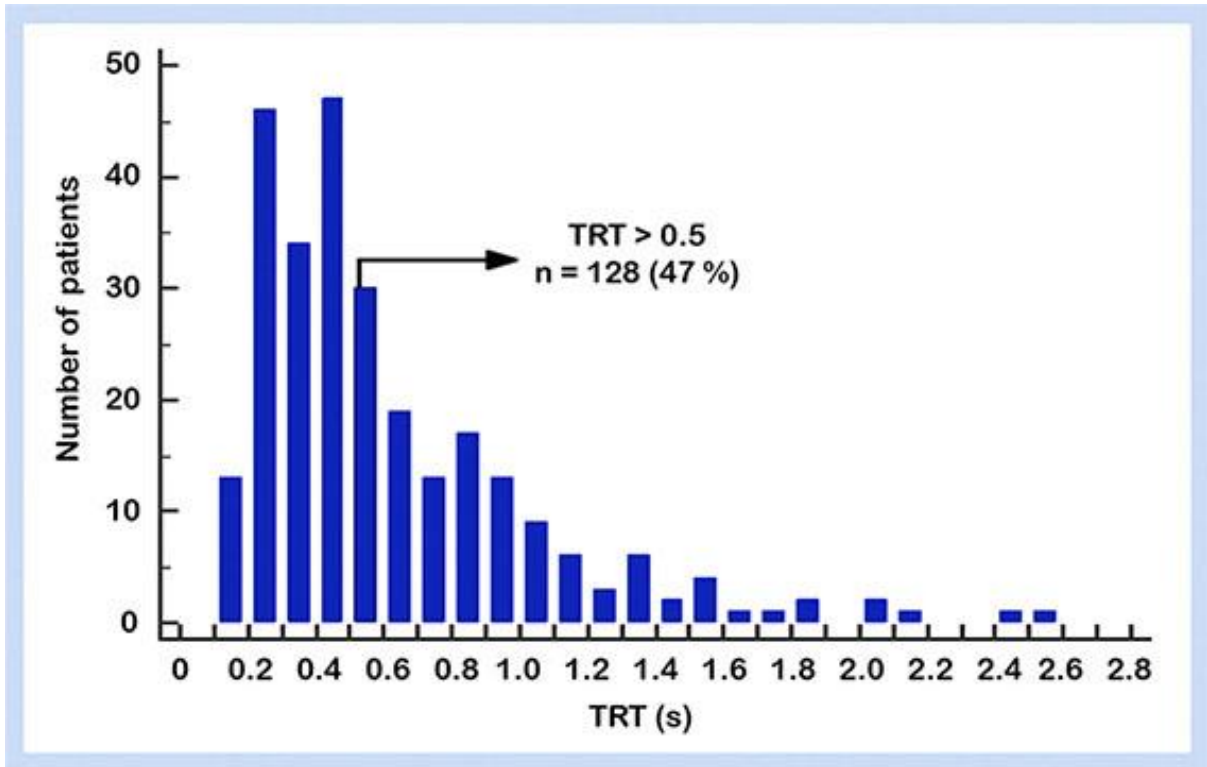
Supplementary Figure 3. From the derivation population, distribution of TRT (temperature recovery time) (n=271).
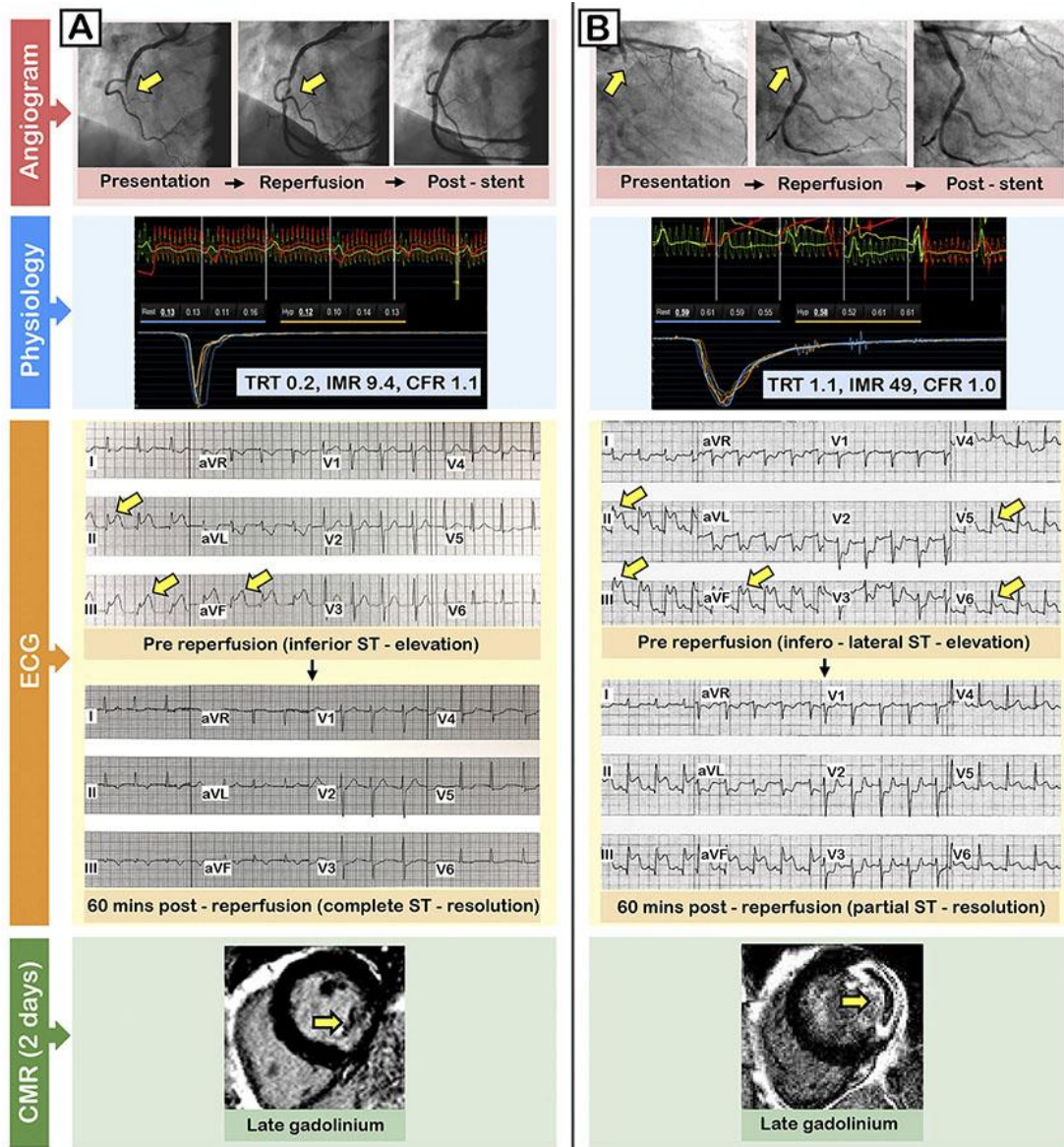
Supplementary Figure 4. Examples of clinical cases.

Two patients with acute ST-segment elevation myocardial infarction (STEMI), treated by primary percutaneous coronary intervention (PCI). Both patients had Thrombolysis In Myocardial Infarction (TIMI) coronary flow grade 3 in the culprit artery, post PCI.

A) Normal TRT (temperature recovery time). The culprit was an occluded right coronary artery. IMR (index of microcirculatory resistance) and TRT were normal, indicating successful myocardial reperfusion. ECGs (electrocardiograms) showed complete resolution of inferior ST-segment elevation. CMR (cardiovascular magnetic resonance) imaging performed two days post STEMI revealed a small subendocardial infarct without MVO (microvascular obstruction).

B) Increased TRT. The culprit was an occluded circumflex artery. Invasively measured microvascular function was abnormal (IMR 49, TRT 1.1), indicating impaired myocardial reperfusion. ECGs showed only partial resolution of inferolateral ST-segment elevation. Two days later CMR imaging revealed MVO. CFR: coronary flow reserve
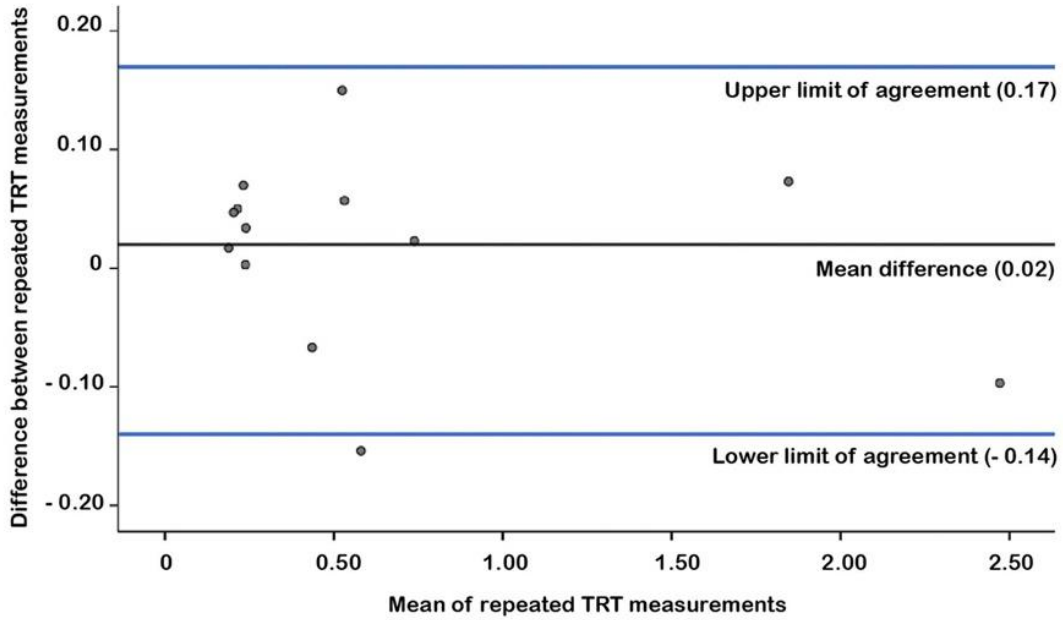
Supplementary Figure 5. Bland-Altman plot of differences plotted against the averages of paired TRT measurements after primary PCI, obtained by four different cardiologists in 13 patients.

Horizontal lines are drawn at the mean difference and at the limits of agreement.

Supplementary Table 1. From the derivation population, summary of logistic and linear regression analyses, showing univariable and multivariable associations (with IMR >40 in multivariable models) between TRT and MVO, all-cause death/heart failure hospitalisations, or major adverse cardiac events.

	Univariable analysis OR/coefficient (95% CI)	*p*-value	Multivariable analysis OR/coefficient (95% CI)	*p*-value
Associations with MVO extent (%LV mass) on CMR 2-7 days post PCI*				
TRT continuous	4.38 (3.07, 5.68)	**<0.001**	4.09 (2.70, 5.48)	**<0.001**
TRT >0.5	2.84 (1.71, 3.97)	**<0.001**	1.70 (0.25, 3.15)	**0.022**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			1.53 (-0.18, 3.23)	0.080

*Other variables in multivariable model: age, ischaemic time, IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with MVO presence on CMR 2-7 days post PCI†				
TRT continuous	5.52 (2.59, 11.77)	**<0.001**	5.26 (2.36, 11.74)	**<0.001**
TRT >0.5	3.36 (2.04, 5.53)	**<0.001**	3.01 (1.75, 5.16)	**<0.001**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			1.72 (0.78, 3.77)	0.178

† Other variables in multivariable model: age, ischaemic time, IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with 30-day mortality or heart failure hospitalisation‡				
TRT continuous	6.64 (2.90, 15.24)	**<0.001**	6.27 (1.89, 20.78)	**0.003**
TRT >0.5	8.14 (2.35, 28.20)	**0.001**	5.77 (1.44, 23.14)	**0.013**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			4.48 (1.14, 17.63)	**0.032**

‡Other variables in multivariable model: IMR >40

Associations with mortality or heart failure hospitalisation at median 5 years§				
TRT continuous	3.85 (1.97, 7.51)	**<0.001**	4.14 (2.08, 8.25)	**<0.001**
TRT >0.5	3.11 (1.63, 5.93)	**0.001**	5.81 (2.16, 15.63)	**<0.001**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			5.37 (2.00, 14.43)	**0.001**

§Other variables in multivariable model: IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with 30-day MACE‡				
TRT continuous	6.51 (2.89, 14.69)	**<0.001**	6.06 (1.88, 19.57)	**0.003**
TRT >0.5	9.16 (2.66, 31.51)	**<0.001**	6.81 (1.74, 26.62)	**0.006**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			5.18 (1.34, 19.99)	**0.017**

Associations with MACE at median 5 years§				
TRT continuous	3.55 (1.79, 7.03)	**<0.001**	4.05 (2.00, 8.21)	**<0.001**
TRT >0.5	2.39 (1.21, 4.71)	**0.012**	2.65 (1.32, 5.30)	**0.006**
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			2.19 (0.76, 6.29)	0.145

CFR: coronary flow reserve; CI: confidence interval; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; LV: left ventricular; MVO: microvascular obstruction; OR: odds ratio; PCI: percutaneous coronary intervention; Tmn: mean transit time; TRT: temperature recovery time

Supplementary Table 2. Summary of logistic and linear regression analyses, showing univariable and multivariable associations (with IMR >32 in multivariable models) between TRT and angiogram parameters at the end of PCI.

DERIVATION COHORT

	Univariable analysis OR/coefficient (95% CI)	*p*-value	Multivariable analysis OR/coefficient (95% CI)	*p*-value
Associations with TIMI frame count at the end of PCI*				
TRT continuous	5.68 (2.34, 9.02)	**0.001**	2.25 (-2.55, 7.04)	0.357
TRT >0.5	3.80 (0.99, 6.61)	**0.008**	-0.58 (-4.68, 3.52)	0.781
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			-1.95 (-6.00, 2.09)	0.343

*Other variables in multivariable model: IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with TIMI coronary flow grade ≤2 at the end of PCI†				
TRT continuous	10.24 (3.84, 27.32)	**<0.001**	12.24 (3.16, 47.41)	**<0.001**
TRT >0.5	7.29 (1.6, 33.25)	**0.010**	4.67 (0.81, 26.82)	0.084
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			1.05 (0.16, 7.03)	0.961

† Other variables in multivariable model: IMR >32

Associations with myocardial perfusion grade ≤1 at the end of PCI‡				
TRT continuous	3.17 (1.69, 5.95)	**<0.001**	2.99 (1.57, 5.68)	**0.001**
TRT >0.5	1.82 (1.06, 3.11)	**0.029**	1.25 (0.55, 2.84)	0.594
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			1.00 (0.43, 2.32)	0.996

‡Other variables in multivariable model: IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

VALIDATION COHORT

	Univariable analysis OR/coefficient (95% CI)	*p*-value	Multivariable analysis OR/coefficient (95% CI)	*p*-value
Associations with TIMI frame count at the end of PCI*				
TRT continuous	15.18 (10.56, 19.79)	**<0.001**	13.49 (6.68, 20.30)	**<0.001**
TRT >0.5	10.98 (6.43, 15.52)	**<0.001**	4.86 (6.59, 15.63)	**<0.001**
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			4.94 (-1.41, 11.29)	0.126

*Other variables in multivariable model: IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with TIMI coronary flow grade ≤2 at the end of PCI†				
TRT continuous	9.42 (3.32, 26.69)	**<0.001**	4.10 (1.26, 13.30)	**0.019**

TRT >0.5	17.55 (2.27, 135.88)	**0.006**	3.86 (0.37, 40.77)	0.262
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			5.33 (0.58, 48.58)	0.138

† *Other variables in multivariable model: IMR >32*

Associations with myocardial perfusion grade ≤1 at the end of PCI‡

TRT continuous	3.30 (1.51, 7.21)	**0.003**	1.36 (0.46, 4.02)	0.578
TRT >0.5	2.72 (1.28, 5.80)	**0.009**	0.92 (0.29, 2.95)	0.895
TRT >0.5 (IMR >32, substituted by continuous IMR in model)			0.80 (0.25, 2.53)	0.698

‡*Other variables in multivariable model: IMR >32, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform*

CFR: coronary flow reserve; CI: confidence interval; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; MVO: microvascular obstruction; OR: odds ratio; PCI: percutaneous coronary intervention; Tmn: mean transit time; TRT: temperature recovery time

Supplementary Table 3. Summary of logistic and linear regression analyses, showing univariable and multivariable associations (with IMR >40 in multivariable models) between TRT and angiogram parameters at the end of PCI.

DERIVATION COHORT

	Univariable analysis OR/coefficient (95% CI)	*p*-value	Multivariable analysis OR/coefficient (95% CI)	*p*-value
Associations with TIMI frame count at the end of PCI*				
TRT continuous	5.68 (2.34, 9.02)	**0.001**	1.00 (-4.32, 6.31)	0.712
TRT >0.5	3.80 (0.99, 6.61)	**0.008**	-1.26 (-5.44, 2.91)	0.552
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			-1.95 (-6.00, 2.09)	0.343

Other variables in multivariable model: IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with TIMI coronary flow grade ≤2 at the end of PCI†				
TRT continuous	10.24 (3.84, 27.32)	**<0.001**	8.65 (2.20, 33.99)	**0.002**
TRT >0.5	7.29 (1.6, 33.25)	**0.010**	3.06 (0.49, 19.00)	0.231
TRT >0.5 (IMR >, substituted by continuous IMR in model)			1.05 (0.16, 7.03)	0.961

† Other variables in multivariable model: IMR >40

Associations with myocardial perfusion grade ≤1 at the end of PCI‡				
TRT continuous	3.17 (1.69, 5.95)	**<0.001**	2.99 (1.57, 5.68)	**0.001**
TRT >0.5	1.82 (1.06, 3.11)	**0.029**	1.14 (0.49, 2.62)	0.767
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			0.92 (0.38, 2.12)	0.855

‡Other variables in multivariable model: IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

VALIDATION COHORT

	Univariable analysis OR/coefficient (95% CI)	*p*-value	Multivariable analysis OR/coefficient (95% CI)	*p*-value
Associations with TIMI frame count at the end of PCI*				
TRT continuous	15.18 (10.56, 19.79)	**<0.001**	12.94 (5.83, 20.05)	**<0.001**
TRT >0.5	10.98 (6.43, 15.52)	**<0.001**	5.88 (-0.56, 12.31)	0.073
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			4.94 (-1.41, 11.29)	0.126

Other variables in multivariable model: IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform

Associations with TIMI coronary flow grade ≤2 at the end of PCI†				
TRT continuous	9.42 (3.32, 26.69)	**<0.001**	6.65 (1.14, 38.95)	**0.038**

TRT >0.5	17.55 (2.27, 135.88)	**0.006**	4.78 (0.48, 47.69)	0.183
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			5.33 (0.58, 48.58)	0.138

† *Other variables in multivariable model: IMR >40*

Associations with myocardial perfusion grade ≤1 at the end of PCI‡

TRT continuous	3.30 (1.51, 7.21)	**0.003**	1.02 (0.33, 3.14)	0.975
TRT >0.5	2.72 (1.28, 5.80)	**0.009**	0.84 (0.26, 2.74)	0.771
TRT >0.5 (IMR >40, substituted by continuous IMR in model)			0.80 (0.25, 2.53)	0.698

‡*Other variables in multivariable model: IMR >40, CFR ≤2, hyperaemic Tmn >median, thermodilution waveform*

CFR: coronary flow reserve; CI: confidence interval; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; MVO: microvascular obstruction; OR: odds ratio; PCI: percutaneous coronary intervention; Tmn: mean transit time; TRT: temperature recovery time

Supplementary Table 4. Characteristics of the validation population.

Validation population characteristics	Overall (n=144)
Age, years	59.4±10.5
Male	115 (79.9)
Current smoker	68 (47.2)
Body mass index, kg/m^2	28.4±5.1
Hypertension	41 (28.5)
Diabetes mellitus	16 (11.1)
Previous myocardial infarction	8 (5.6)
Presenting heart rate, beats per minute	73.0±15.1
Presenting systolic blood pressure, mmHg	139.7±26.1
Ischaemic time, hours, median (IQR)	2.8 (2.0-3.8)
Baseline creatinine, μmol/L	79.5±15.5
Procedural characteristics	
Culprit artery:	
Left anterior descending	54 (37.5)
Circumflex	24 (16.7)
Right coronary artery	66 (45.8)
Number of main vessels diseased	
1	83 (57.6)
2	49 (34.0)
3	12 (8.3)
Thrombus aspiration	23 (16.0)
Glycoprotein IIb/IIIa inhibitor	8 (5.6)
Study drug received:	
Alteplase 20 mg	50 (34.7)
Alteplase 10 mg	41 (28.5)
Placebo	53 (36.8)

Data are mean±SD, or n (%), unless otherwise stated.

Missing: creatinine, n=1.

IQR: interquartile range; PCI: percutaneous coronary intervention; SD: standard deviation

Supplementary Table 5. From the validation population, electrocardiogram, angiogram, and coronary physiology parameters on admission and CMR findings at 2-7 days after PCI for STEMI.

Validation population parameters	Overall (n=144)
Electrocardiogram	
ST-segment resolution:	
Complete, ≥70%	50 (35.5)
<70%	91 (64.5)
Angiogram	
Initial TIMI coronary flow grade:	
0	114 (79.2)
1	14 (9.7)
2	16 (11.1)
Final TIMI coronary flow grade:	
1	3 (2.1)
2	15 (10.4)
3	126 (87.5)
TIMI frame count post PCI, median (IQR)	18.0 (14.0-26.0)
Myocardial perfusion grade post PCI:	
≤1	45 (31.3)
≥2	99 (68.8)
Coronary physiology post PCI	
Pa, mmHg, median (IQR)	76.0 (66.0-86.0)
Pd, mmHg, median (IQR)	69.0 (60.0-78.0)
TRT, median (IQR)	0.5 (0.3-1.0)
TRT >0.5	79 (54.9)
IMR, median (IQR)	29.5 (17.0-55.0)
IMR >32	69 (47.9)
IMR >40	57 (39.6)
CFR, median (IQR)	1.4 (1.1-2.0)
CFR ≤2	115 (79.9)
Hyperaemic Tmn, median (IQR)	0.4 (0.3-0.8)
Hyperaemic Tmn >median	69 (47.9)
Waveform:	
Bimodal	13 (9.0)
Wide unimodal	56 (38.9)
Wide bimodal	75 (52.1)
CMR 2-7 days post PCI	
MVO extent (% left ventricular mass)	0.0 (0.0-3.3)
MVO present	57 (41.0)

Data are mean±SD, or n (%) unless otherwise stated.
Missing: MVO, n=5; ST-segment resolution, n=3.

CFR: coronary flow reserve; CMR: cardiovascular magnetic resonance; IMR: index of microcirculatory resistance; IQR: interquartile range; MVO: microvascular obstruction; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; Tmn: mean transit time; TRT: temperature recovery time