Spontaneous reperfusion in patients with transient ST-elevation myocardial infarction - *prevalence, importance and approaches to management*

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Abstract

Patients with transient ST-elevation myocardial infarction (STEMI) or spontaneous resolution (SpR) of the ST-segment elevation on electrocardiogram could potentially represent a unique group of patients posing a therapeutic management dilemma. In this review, we discuss the potential mechanisms underlying SpR, its relation to clinical outcomes and the proposed management options for patients with transient STEMI with a focus on immediate versus early percutaneous coronary intervention. We performed a structured literature search of PubMed and Cochrane Library databases from inception to December 2020. Studies focused on SpR in patients with acute coronary syndrome were selected. Available data suggest that deferral of angiography and revascularisation within 24-48 hours in these patients is reasonable and associated with similar or perhaps better outcomes than immediate angiography. Further randomized trials are needed to elucidate the best pharmacological and invasive strategies for this cohort.

Key words myocardial infarction, spontaneous resolution, percutaneous coronary intervention, outcome

Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
GPI	glycoprotein IIb/IIIa inhibitors
IRA	infarct-related artery
MACE	major adverse cardiac events
NSTE-ACS	non-ST-elevation acute coronary syndrome
PCI	percutaneous coronary intervention
PPCI	primary percutaneous coronary intervention
SpR	spontaneous resolution
STEMI	ST-elevation myocardial infarction

Introduction

Myocardial ischaemia presents when metabolic demands of the myocardium outweigh the supply of oxygen through the coronary arteries. Complete cessation of blood flow due to acute formation of a persistent occlusive arterial thrombus gives rise to transmural myocardial infarction characterized typically by chest discomfort, development of ST-segment elevation on the electrocardiogram and rise in myocardial enzymes. A significant proportion of patients presenting with ST-elevation myocardial infarction (STEMI) demonstrate an abrupt resolution of the ST-segment elevation on electrocardiogram (Figure 1) coinciding with restoration of flow in the occluded epicardial artery, also known as reperfusion, which is frequently associated with resolution or improvement of symptoms (1). Reperfusion, occurring either spontaneously or after initial pharmacotherapy, but before revascularization, is also termed "transient STEMI" and is different from the ST-segment resolution that usually follows timely reperfusion therapy (primary percutaneous coronary intervention [PPCI] or thrombolysis). The latter has been assessed in various clinical studies as a surrogate endpoint (2–4) and is out of the scope of this review. Transient ST-segment elevation on electrocardiogram has also been described in many conditions other than acute myocardial infarction, such as coronary spasm (5–9). The present review focuses on the spontaneous ST-segment resolution that occurs in patients with STEMI due to atherosclerotic plaque disruption and overlying thrombotic occlusion.

Transient STEMI or spontaneous resolution (SpR) of STEMI is a clinical phenomenon generally defined as greater than 50% resolution of ST-segment elevation on two consecutive electrocardiograms accompanied by significant improvement in chest pain and angiographically Thrombolysis in Myocardial Infarction (TIMI) flow grade 2-3 before any PPCI or thrombolysis (10,11). The frequency of SpR in STEMI patients at angiography was

first reported in a pioneering study published by De Wood and colleagues in 1980. In this study, SpR defined as any forward flow in the infarct-related artery (IRA) was demonstrated in 12.7% of STEMI patients within 4 hours of the onset of chest pain (12). In 585 STEMI patients randomized to the PPCI arm of the ASsessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT 4 PCI) study, it was demonstrated that SpR had a frequency of 14.7% and 14.9% using angiographic and electrocardiographic criteria, respectively (1). Most studies have since yielded similar results, with SpR prevalence averaging around 15% in STEMI patients (1,13–17).

In patients with STEMI, the recommended optimal treatment to achieve reperfusion is emergency PCI (18,19). In patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), a delayed invasive approach is recommended for up to 72 hours in those without high-risk features (20,21). Transient STEMI seems to be a unique condition with recent ESC guidelines suggesting an early, but not immediate, invasive approach with a view to revascularization within 24 hours of presentation (20). It is not clear whether patients with transient STEMI due to SpR should be treated in a similar fashion to those with STEMI. Although theoretically, these patients may benefit from emergency PCI potentially to reduce or limit infarct size or prevent the progression to persistent STEMI with all subsequent complications, an immediate invasive strategy did not reduce infarct size as assessed by consequent infarct volume on cardiac magnetic resonance imaging, compared with an early invasive strategy within 24 hours of presentation (22). Moreover, an early approach may indeed be more appropriate to allow time for initial pharmacological interventions to stabilize the ruptured plaque and reduce thrombus burden, which may help to reduce the occurrence of microvascular occlusion during subsequent PCI.

Understanding the mechanisms underlying SpR is therefore important, since this may not only improve management strategies, but also identify possible novel therapeutic targets. In this review, we discuss the potential mechanisms, clinical outcomes and contemporary management of transient STEMI due to SpR.

Methods

The study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. We performed a structured literature search of the PubMed and the Cochrane Library databases from inception to December 2020. We used an advanced search strategy utilizing the terms, spontaneous resolution or transient, and myocardial infarction or acute coronary syndrome. Two reviewers (MF and MP) independently performed the search and literature screen, with disputes resolved by consensus following discussion with other authors (NS and YG). Studies focused on SpR in patients with acute coronary syndrome (ACS) and reporting clinical outcomes were selected (Supplemental Figure 1). Relevant data was extracted and synthesized for narrative review.

Transient STEMI and clinical outcomes

A summary of available studies reporting clinical outcomes with transient STEMI is shown in Table 1. All patients had a diagnosis of acute myocardial infarction with elevated cardiac biomarkers. Most studies demonstrated that patients presenting with signs of SpR are less likely to be in heart failure with less myocardial damage on admission (11,23,24) and have better in-hospital (25,26) and long-term clinical outcomes (1) compared to those without SpR.

The impact of SpR on clinical outcomes has been widely investigated with promising results. In a landmark study examining the outcome of STEMI patients with angiographically

proven SpR who were conservatively managed without emergency PCI, the risk of recurrent ischaemia was similar in the SpR cohort compared to those receiving thrombolysis or PPCI (27). In addition, the SpR group had lower peak creatine kinase levels with better left ventricular ejection fraction than those receiving thrombolysis or PPCI (56.4% vs. 47.9% and 48.7%, respectively). In 196 patients undergoing PPCI, those with angiographic evidence of SpR (n=44) were more likely to be in Killip class ≤2 on admission, had significantly lower rates of congestive heart failure (2.3% vs. 15.1%, P<0.05) and primary ischaemic outcome occurrence (4.5% vs. 18.4%, P<0.05) compared with patients without SpR (n=152) (28). Similarly, in 2,507 patients enrolled in the Primary Angioplasty in Myocardial Infarction (PAMI) Trials and undergoing PPCI, 6-month mortality was lowest in patients with SpR and initial TIMI flow grade 3 compared to patients with initial TIMI flow grade 0-2 (26). More recently, on analysing the combined data sets of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) and the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials, angiographically-defined SpR was an independent predictor of 1-year survival in 5,332 patients undergoing PPCI (29). Furthermore, amongst 1,727 consecutive ACS patients, those with transient STEMI (n=126) had lower long-term mortality at a median follow up of 36 months compared to both persistent STEMI (n=1,073) and non-STEMI (n=649) patients (15). Finally, in the RISK-PPCI study, we found that 74 (14.9%) of 496 STEMI patients had spontaneous ST-segment resolution on electrocardiogram prior to PPCI, with only 2 patients experiencing recurrent non-index IRA myocardial infarction at 12 months follow-up (14).

Determinants of spontaneous reperfusion

1) Endogenous fibrinolysis

The active inflammatory process leading to the formation of atherosclerotic plaques has been extensively described in literature (30,31). In the vast majority of STEMI cases, coronary thrombi form on top of a ruptured or fissured atherosclerotic plaque (32). The three main determinants of the thrombotic response to plaque rupture are 1) endothelial injury or dysfunction, 2) flow disturbances including stasis or shear stress, and 3) the dynamic equilibrium between thrombotic and thrombolytic forces (33). The major thrombogenic components contained within the atherosclerotic plaque include soluble agents such as tissue factor and collagen, thought to be highly thrombogenic (34). The thrombogenicity of this substrate, along with high arterial shear stress, which is maximal at sites of luminal narrowing (35), lead to platelet activation and aggregation with the formation of a platelet-rich thrombus protruding into the vessel lumen (36). In parallel, activation of coagulation results in the formation of fibrin, which imparts stability to the growing platelet thrombus, and which, together with platelets, plays a crucial role in persistent arterial occlusion. An active and functioning endogenous fibrinolytic system is imperative for the prevention of occlusive thrombus formation and lasting vessel occlusion. Endogenous fibrinolysis is achieved through conversion of plasminogen to plasmin by endovascular tissue plasminogen activator resulting in the breakdown of fibrin into fibrin degradation products.

Thrombus formation is a dynamic process continuously shifting between thrombotic and fibrinolytic processes. If thrombotic drivers prevail, lasting vessel occlusion occurs and in contrast, if the fibrinolytic drivers prevail, SpR occurs. Previous research has focused predominantly on achieving reperfusion with pharmacological fibrinolysis or mechanical

means, or pharmacological modulation of platelet reactivity and coagulation factors in preventing further intra-luminal thrombosis. However, there is emerging evidence to suggest that ACS is a result of failure of endogenous fibrinolysis (37). Kramer and colleagues investigated aspirated intra-luminal thrombi of 1009 STEMI patients and found that 40% of patients (n=382) demonstrated lytic (>24 hours) or organised (>5 days) thrombi signifying that thrombus formation occurred significantly earlier than the time of onset of symptoms and as an indication of inadequate endogenous fibrinolysis (38). In our RISK-PPCI study, severely impaired endogenous fibrinolysis as evidenced by a prolonged lysis time measured in whole blood *in vitro*, was detected in 14% of patients and was an independent predictor of major adverse cardiovascular events (MACE), while approximately 15% of patients demonstrated very rapid endogenous fibrinolysis, which was predictive of very low cardiovascular risk (14). Increasing lysis time *in vitro* was associated with increasing density of the fibrin network. A substudy of the PLATelet inhibition and patient Outcomes (PLATO) trial found that plasma clot lysis time independently predicts the risk of spontaneous myocardial infarction and cardiovascular death at 1-year follow up (39). Each 50% increase in lysis time resulted in an increased risk of adverse outcomes.

In a substudy of 683 STEMI patients in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX AMI) trial (23), 290 patients had SpR defined as pre-PPCI TIMI flow grade 2-3. SpR was found to be associated with multiple proteins across different pathobiological pathways. Elafin, matrix metalloproteinase 3 (MMP3), kallikrein-6 (KLK-6), and matrix extracellular phosphoglycoprotein (MEPE) most strongly correlated with pre-PPCI TIMI flow. The pathophysiologic role of these proteins and their correlation to SpR is only partly understood. Elafin appears to play a key role in the endogenous inhibition of immunothrombotic pathways driven by neutrophil activation. The inhibition of these pathways has previously been shown to favourably affect infarct size, ischaemia-reperfusion and arterial

injury (40). MMP3 has been shown in preclinical models to hydrolyse plasminogen and urokinase-type plasminogen activator suggesting a role in facilitating endogenous fibrinolysis (41). The mechanisms underlying the correlation between KLK-6 and MEPE and SpR remain unclear.

2) Extent of coronary disease

A series of observational studies involving patients with ACS found that patients presenting with transient STEMI more often have underlying single-vessel CAD compared to those with other ACS presentations (42–44). In 62 patients with transient STEMI, single-vessel CAD constituted 60% of cases with a lower atherosclerotic burden compared with 62 matched STEMI controls (16). Amongst 83 STEMI patients with and without SpR, those without SpR more often had multivessel disease than those with SpR (45). In a cohort of 469 patients with STEMI, the 77 patients who had SpR more frequently had distal coronary culprit lesions (46).

3) High shear stress

The main determinant of platelet activation and aggregation in stenosed arteries is shear stress (maximal at the centre of the lumen) and wall shear rate (maximal near the periphery of the vessel wall). Shear stress increases almost exponentially with the degree of luminal stenosis, with values of 0.35–70 dynes/cm^2 in the healthy arteries, rising to 1,500-10,000 dynes/cm^2 in stenosed vessels (47). The increase in platelet recruitment and adhesion at high shear rates, with increased platelet activation by high shear stress, is the main precipitant of thrombosis in stenosed arteries, with soluble agonists generated at the site of vascular injury playing a secondary role in stabilising the growing thrombus (48). High shear rate conditions have an impact not only on growth rate, but also on structure and stability of the forming thrombus (49). Platelet deposition rate gradually increases with increasing wall shear rate

possibly secondary to an increase in the blood volume perfused (50) and/or platelet collision frequency (51). Thrombi forming at higher wall shear rates (>5000 s^{-1}) predominantly consist of large thick platelets characterized by a tightly packed core and thicker shell (52). The stability of the arterial thrombus determines the degree and duration of occlusion resulting in different clinical pictures and variable extent of myocardial tissue damage (53). Elevated wall shear rate and increasing thrombus volume may inadvertently increase the likelihood of thrombus detachment from the vessel wall, resulting in downstream embolization and/or fibrinolysis (52,54,55). Wall shear rates and shear stress may therefore be pivotal not only in forming but also relieving persistent arterial occlusion (49).

4) Initial pharmacological interventions to influence reperfusion

Aspirin and $P2Y_{12}$ inhibitors

Prior aspirin users appear to have less severe types of ACS at presentation compared with non-aspirin users (56), suggesting that platelet inhibition by prior aspirin may mitigate against persistent vessel occlusion. In the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT 4 PCI) trial, and amongst 585 STEMI patients randomized to the PPCI arm, those who achieved angiographic SpR were more likely to have been prior aspirin users (1). Optical coherence tomography of the culprit lesion in 442 patients with first ACS presentation found less frequent and smaller thrombi in those with a history of chronic aspirin use (57), with STEMI presentation being significantly less frequent in aspirin users than non-users (20.9% vs. 46.4%, P<0.001). Furthermore, a history of pre-admission antiplatelet therapy (aspirin or a thienopyridine) was an independent predictor of preprocedural TIMI flow grade 3 in 2,182 patients presenting with STEMI (25).

In the ST-MONitoring in Acute Myocardial Infarction (MONAMI) study, treatment with

aspirin and clopidogrel before transfer to the interventional hospital might have contributed to the high incidence of SpR observed in 92 STEMI patients undergoing PPCI (24). Similarly, another study hypothesised that timely administration of aspirin and clopidogrel may induce SpR in patients with STEMI (16). In the Early Thienopyridine treatment to improve primary PCI in Patients with Acute Myocardial Infarction (ETAMI) trial, loading with 60mg prasugrel did not appear to increase IRA patency pre-PPCI compared to 600mg clopidogrel (59). However, the median time between the study drug and angiography in the two randomized groups was only 15 and 23 minutes, respectively, probably too short to see an impact on reperfusion. Analysis of STEMI patients from the French national prospective multicentre registry (FAST-MI 2010) (60) showed that pre-treatment with prasugrel or glycoprotein IIb/IIIa inhibitors (GPI) was independently associated with higher IRA patency rates. Furthermore, the association between early administration of rapid-onset antiplatelet agents and IRA patency was found to progressively increase as time from qualifying electrocardiogram to angiography increased, suggesting a role for early administration of rapid-onset antiplatelet therapy in achieving SpR.

Glycoprotein IIb/IIIa inhibitors (GPI)

Administration of abciximab, compared to placebo, has been shown to be associated with greater frequency of pre-PPCI TIMI flow grade 2-3 in 300 patients with STEMI (61). Subsequent studies found that early administration of abciximab, before arrival in the catheterization laboratory, increased the incidence of early recanalization of the IRA and improved pre-PPCI angiographic findings compared with late administration (62–65). Moreover, early abciximab administration appears to correlate with markers of effective reperfusion at tissue level as evidenced by greater ST-segment resolution on electrocardiogram and improved myocardial blush grade (63,64). However, routine prehospital administration of

abciximab before PPCI has not been demonstrated to improve clinical outcomes owing to an increased bleeding risk compared with restricted use for bailout (66). Similarly, prehospital administration of tirofiban has been shown to significantly improve ST-segment resolution both before (67) and after PPCI in patients with STEMI (68). A meta-analysis of 6 randomized trials including 2,197 patients comparing the use of abciximab with small molecule GPI (eptifibatide and tirofiban) in PPCI, showed no difference in angiographic, electrocardiographic, and clinical outcomes, suggesting a class-effect (69).

Anticoagulants

Prehospital administration of UFH (≥5,000 IU IV) was associated with greater IRA patency rates compared to in-hospital administration in STEMI patients (70). Similar results were seen with prehospital administration of enoxaparin in STEMI patients in a subsequent study investigating the effect of early versus late heparin administration on initial IRA patency and clinical outcomes (71). In the early heparin group, either UFH or enoxaparin were administered 144±95min before angioplasty, whereas in the late heparin group, UFH was administered immediately prior to PPCI. Compared to the late heparin group, initial TIMI flow grade 2 or 3 was more frequent in the early heparin group (48% vs. 22%, P=0.002), TIMI flow grade 3 was also more frequent (41% vs. 11%, P<0.001) and TIMI flow grade 0 was less frequent (48% vs. 70%, P=0.014), respectively. However, these benefits were not seen to reduce MACE. Similar time-dependent, beneficial effects of heparin on IRA patency were seen in a few other studies (72,73). Another study comparing pre-PPCI TIMI flow in STEMI patients receiving prehospital heparin and a GPI versus those receiving bivalirudin and a GPI showed similar results (74).

Opioids

The interaction between opioids and $P2Y_{12}$ inhibitors has been well documented in the literature, with evidence suggesting that intravenous opioids reduce the absorption of oral antiplatelet agents by slowing gastric emptying (75,76). A few studies suggest a trend towards impaired IRA reperfusion pre-PPCI in morphine-treated STEMI patients. The ATLANTIC trial showed that STEMI patients receiving prehospital morphine were less likely to achieve the electrocardiogram primary end point of ST-segment resolution ≥70% pre-PPCI compared with patients not treated with morphine (58). In another study, there was a trend towards a greater rate of TIMI flow grade 2-3 pre-PPCI in those who did not receive morphine compared to those who did (55.6% vs. 44.7%, P=0.09) (77). In 182 STEMI patients receiving either prasugrel (n=51) or ticagrelor (n=131), TIMI flow grade <2 was more frequent amongst patients treated with morphine (79% vs. 64%, P=0.036). Morphine-treated patients were seen to have a larger infarct size, as evidenced by significantly higher creatine phosphokinase peak compared with morphine-naïve patients (2). In our study of 300 STEMI patients, complete ST-segment resolution prior to PPCI was far less frequently observed (9.2% vs. 31.7%, P<0.001) and angiographic flow in the IRA was significantly reduced pre-PPCI (21.6% vs. 48.8%, P=0.001) amongst patients who had received morphine (n=218) compared with those who had not. Interestingly, this effect was negated by concomitant GPI (78).

Transient STEMI and timing of angiography

The optimal timing of angiography and coronary intervention for patients with transient STEMI is not clear. A study which compared 69 transient STEMI patients treated with intense antithrombotic therapy followed by an invasive approach at a median time of 36 hours after presentation, with patients without SpR treated with convention medical treatment and emergency revascularisation, showed that patients with clinical and electrocardiographic evidence of SpR had less extensive CAD, higher TIMI flow grade in the IRA, less myocardial

damage and better cardiac function, indicating that an intense medical therapy with an early invasive approach may be an appropriate therapy in this cohort (16). In another study of 710 STEMI patients, of whom 22% (n=155) showed clinical evidence of SpR, only 8% (n=13) underwent emergency PPCI compared to 94% (n=523) of patients without SpR, and yet the SpR cohort had better in-hospital outcomes with lower incidence of congestive heart failure, cardiogenic shock, malignant arrhythmias and in-patient mortality (13). However, a trend towards a higher incidence of the composite adverse outcome of 30-day mortality, congestive heart failure, and/or recurrent ACS was noted amongst patients with SpR undergoing deferred coronary angiography ≥48 hours after admission, resulting in the recommendation to perform coronary angiography within the first 48 hours of admission. In a later study enrolling 2,361 STEMI patients, the same group found that the outcomes of patients undergoing deferred coronary angiography in the presence of clinical evidence of SpR (more than 24/48 hours after admission) were equivalent to those undergoing early angiography (<24 hours after admission), suggesting that deferred intervention may be a safe approach in this cohort of patients (79).

In a small observational study of 86 patients with transient STEMI, there was no difference in 30-day MACE, but there was a higher incidence of angina and myocardial infarction in those undergoing early (<24 hours from pain onset) compared to those undergoing delayed (>24 hours) PPCI (80). Another small observational study of 78 transient STEMI patients undergoing immediate versus delayed PPCI showed a higher procedural success rate in the delayed PCI group (95% vs. 77%, P=0.008), with no difference in MACE or bleeding complications between groups (81). In the first randomized clinical trial comparing the outcomes of immediate versus delayed invasive strategy in 142 patients admitted with transient STEMI, infarct size measured by cardiac magnetic resonance on day 4 was small and not different between the immediate group and the delayed group (1.3% vs. 1.5%, respectively,

P=0.48). Moreover, there was no difference in 30-day MACE (2.9% vs. 2.8% respectively, P=1.00) (22) or 1-year MACE (4.4% vs. 5.7% respectively, P=1.00) (82), advocating for the interchangeability of a STEMI- or non-STEMI-like approach in patients presenting with transient STEMI (Figure 2).

Limitations

Our review has several limitations. First, all included studies in Table 1 are subjected to all the limitations of the retrospective observational design, such as selection bias. Second, it is possible that many included patients had unobstructed coronary arteries on angiography raising the suspicion of other alternative diagnoses, such as myocarditis or coronary spasm. Third, included studies had different angiographic and/or ECG cut-off values to define STEMI and /or SpR (Table 1). Finally, it is possible that some studies that investigated SpR in patients with STEMI due to atherosclerotic plaque disruption and overlying thrombotic occlusion have been missed.

Conclusions

Understanding the aetiology of SpR in STEMI is important, as this may help to improve the management of both those with and without persistent STEMI (Figure 3. Central Illustration). ACS patients presenting with transient STEMI generally represent a unique group that has not been formally classified as separate from either STEMI or NSTE-ACS patients. The data appear to show that deferral of angiography and revascularisation within 24-48 hours

is reasonable and associated with similar or perhaps better outcomes than immediate angiography, although clearly the limitations of the mainly observational studies and the likely exclusion of relatively high-risk patients, limit any definitive conclusions. Further randomized trials are needed to elucidate the best pharmacological and invasive strategies for this cohort.

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Table 1: Studies reporting transient STEMI due to spontaneous resolution

Study/ year	Patients (n)	Criteria for SpR	SpR (%)	Differences in clinical characteristics between patients with and without SpR	Clinical outcomes between patients with and without SpR
De Wood et al./ 1980 (12)	322	Angiographic (any flow)	7.8%	No differences	Complete coronary occlusion is frequent during early hours of STEMI and decreases during first 24 hours of infarct due to SpR (87.3% 0-4 hours vs. 85.3% 4-6 hours vs. 68.4% 6-12 hours vs. 64.9% 12-24 hours, P<0.01)
Steg et al./ 1997 (27)	325	Angiographic (TIMI=3)	13.3%	No differences	Patients with SpR had smaller infarctions as evidenced by lower peak CK and higher radionuclide LVEF
Christian et al./ 1998 (83)	21	Angiographic (TIMI 1-3)	57%	No differences	Patients with SpR had greater myocardial salvage with smaller infarct size
Ross et al./ 1999 (84)	304	Angiographic (TIMI=3)	15%	No differences	Patients with SpR had greater global ejection fraction and smaller infarct size
Lee et al./ 2001 (28)	196	Angiographic (TIMI≥2)	22.4%	No differences	Patients with SpR had less congestive heart failure at 6-week follow up and so did the primary endpoint of death, reinfarction or congestive heart failure
Stone et al./ 2001 (26)	2,507	Angiographic (TIMI=3)	16%	Patients with SpR were more often female (31.5% vs. 24.8%, P=0.007)	TIMI-3 flow before PCI was an independent determinant of survival
Rimar et al./ 2002 (11)	2,382	ECG (>50% ST-segment resolution)	4.0%	Patients with SpR had a higher prevalence of hypertension and were more likely to have been taking ACE inhibitors	Patients with SpR had lower peak CK and were more likely to develop non-Q wave myocardial infarction. Mortality at 30 days and 1 year was significantly lower for SpR patients and SpR was a strong determinant of 30-day survival

Terkelsen et al./ 2006 (24)	92	ECG (≥70% ST-segment resolution)	23.9%	No differences	SpR patients had lower NT-proBNP levels and better LVEF at 3 months
Bainey et al./ 2008 (1)	585	Angiographic (TIMI=3) or ECG (≥70% ST-segment resolution)	14.7% 14.9%	Patients with angiographic SpR were more often female (32.6% vs. 21%, P<0.03) and were more likely to have prior diabetes (25.6% vs. 14.2%, P<0.03), aspirin use (29.1% vs. 15.9%, P<0.03) and be in Killip class I (98.8% vs. 93%, P<0.03)	Patients with ECG SpR had significant reduction in the composite endpoint of death/reinfarction (0% vs 5.6%, P=0.014) compared with patients without SpR. No differences were evident in patients with angiographic SpR
Meisel et al./ 2008 (16)	112	Complete resolution of ECG changes and full resolution of symptoms	15.1%	No differences	Patients with SpR had less regional wall movement abnormalites on ECG compared with conventional STEMI patients
Leibowitz et al./ 2008 (46)	469	Symptomatic relief and ECG (≥50% ST-segment resolution)	16.4%	Patients with SpR were younger (55±12 vs. 59±13, P<0.03)	Patients with SpR had lower peak CK
Fefer et al./ 2009 (13)	710	ECG (≥70% ST-segment resolution) and ≥70% reduction in pain (assessed using a visual analog score of 0 to 10)	21%	Patients with SpR had more dyslipidemia (65% vs. 52%, P<0.01) and more elevated systolic blood presure (142±29 vs. 135±28 mmHg, P=0.01)	Patients with SpR had lower in-hospital incidence of congestive heart failure (5% vs. 16%, P<0.001), cardiogenic shock (0.7% vs. 8.5%, P<0.001) and all-cause mortality (0% vs. 5%, P<0.01) compared with no-SpR
Brener et al./ 2011 (29)	5,332	Angiographic (TIMI=3)	17.5%	Patients with SpR had more diabetes (20.6% vs. 15.5%, P<0.001), previous myocardial infarction (14.3% vs. 11.2%, P=0.005) and peripheral vascular disease (5.4% vs. 3.4%, P=0.006)	At 1 year, patients with SpR had lower rates of all-cause mortality (2.7% vs. 4.3%, P=0.02) and cardiac mortality (1.3% vs. 2.9%, P=0.04) compared with no-SpR. A 39% RRR in 1-year mortality was observed in patients with SpR

Bailleul et al./ 2016 (60)	1,458	Angiographic (TIMI 2-3)	32%	Patients with SpR had a shorter time from symptom onset to qualifying ECG (110 vs. 135 min, P=0.002) and a longer time from ECG to angiography (105 vs. 93 min, P<0.001)	Mortality at 30 days was significantly lower in patients with SpR compared to no-SpR (0.9% vs. 3.1%, P=0.008). SpR patients had better LVEF
Fefer et al./ 2017 (79)	2,361	ECG (≥70% ST-segment resolution) and ≥70% reduction in pain (assessed using a visual analog score of 0 to 10)	17%	Patients with SpR had more prior angina pectoris (OR 1.38, 95% CI 1.08-1.78) and renal insufficiency (OR 1.72, 95% CI 1.06-2.78). Time from symptom onset to first medical contact was significantly longer in patients with SpR (297±677 vs. 184±457 min, P=0.006) compared with no-SpR patients	Patients with SpR had lower incidence of heart failure (4% vs. 11%, P<0.001) and cardiogenic shock (0% vs. 2%, P=0.001), lower peak CK level and higher LVEF. 30-day and 1-year MACE were equivalent between the groups
Hashimoto et al./ 2018 (25)	2,182	Angiographic (TIMI=3)	14.2%	Patients with SpR had higher systolic blood pressure (143±34.1 vs. 135±33 mmHg, P<0.001) and heart rate (80.8 vs. 77.3 bpm, P=0.008) with more use of antiplatelet therapy (26.5% vs. 19.5%, P=0.005) and beta-blockers (13.9% vs. 10%, P=0.04) on admission compared with no-SpR patients	Patients with SpR were more likely to have post-procedural TIMI 3 flow (P<0.001). SpR was associated with a decrease in VT/VF (2.3% vs. 4.8%, P=0.049) and lower in-hospital mortality (3.6% vs. 7.1%, P=0.02).
Blondheim et al./ 2018 (15)	1,848	ECG (≥90% ST-segment resolution)	6.8%	Patients with SpR were younger, more frequently male and smokers, but had a lower incidence of hypertension and diabetes	Patients with SpR had shortest hospital stay with a significantly lower in-hospital and long-term (median 36 months) mortality and with less anterior myocardial infarcts compared with patients with no-SpR. Patients with SpR had lower peak CK and TnT levels and higher LVEF
RISK-PPCI/ 2019 (14)	496	ECG (either complete (≥70%) or partial (30–70%) ST-segment resolution)	15%	No differences	Patients with SpR had lower MACE at 1 year

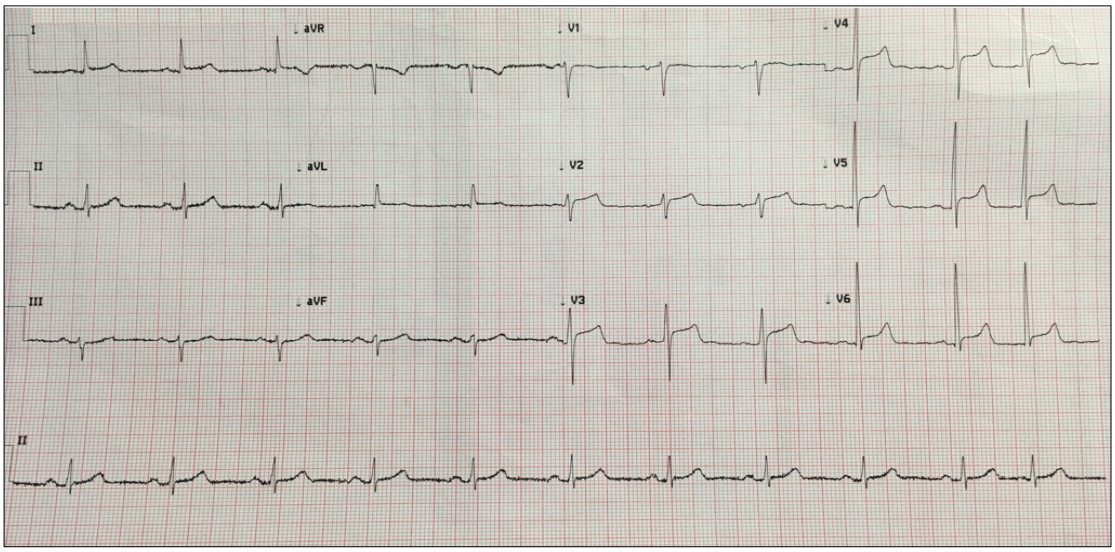
Shavadia et al./ 2020 (23)	683	Angiographic (TIMI 2-3)	42.5%	No differences	SpR was associated with lower frequency of the 90-day composite of death, cardiogenic shock, or congestive heart failure (4.8 vs. 14.8 %, P<0.0001). Patients with SpR were less likely to be in Killip class >1 (8.6% vs. 14.2%, P=0.025) with less TnI and CK levels

ACE: angiotensin converting enzyme, CI: confidence interval, CK: creatinine kinase measured in IU/L, ECG: electrocardiogram, LVEF: left ventricular ejection function, MACE: major adverse cardiac events, OR: odds ratio, RRR: relative risk reduction, STEMI: ST-elevation myocardial infraction, SpR: spontaneous reperfusion, TIMI: thrombolysis in myocardial infarction, TNI: troponin I measured in IU/L, TNT: troponin T measured in IU/L, VF: ventricular fibrillation, VT: ventricular tachycardia

Figure 1. Transient anterior STEMI and complete (>70%) ST-segment resolution prior to emergency revascularization

(A) Electrocardiogram [ECG] taken in the Emergency Department at the onset of chest pain, and (B) ECG repeated in the catheterization laboratory 23 minutes after the first ECG, before angioplasty and when chest pain had resolved. The patient had a ruptured plaque in proximal left anterior descending artery (LAD) with TIMI III flow in distal vessel and underwent percutaneous coronary angioplasty with a single drug-eluting stent, with no complications.

(A)



(B)

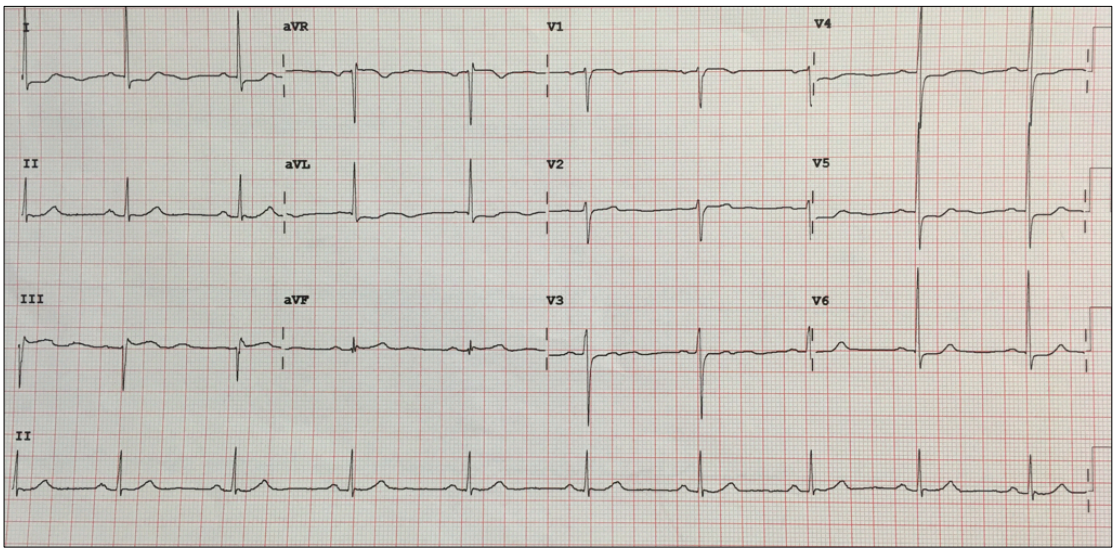


Figure 2. Studies evaluating transient STEMI and timing of intervention

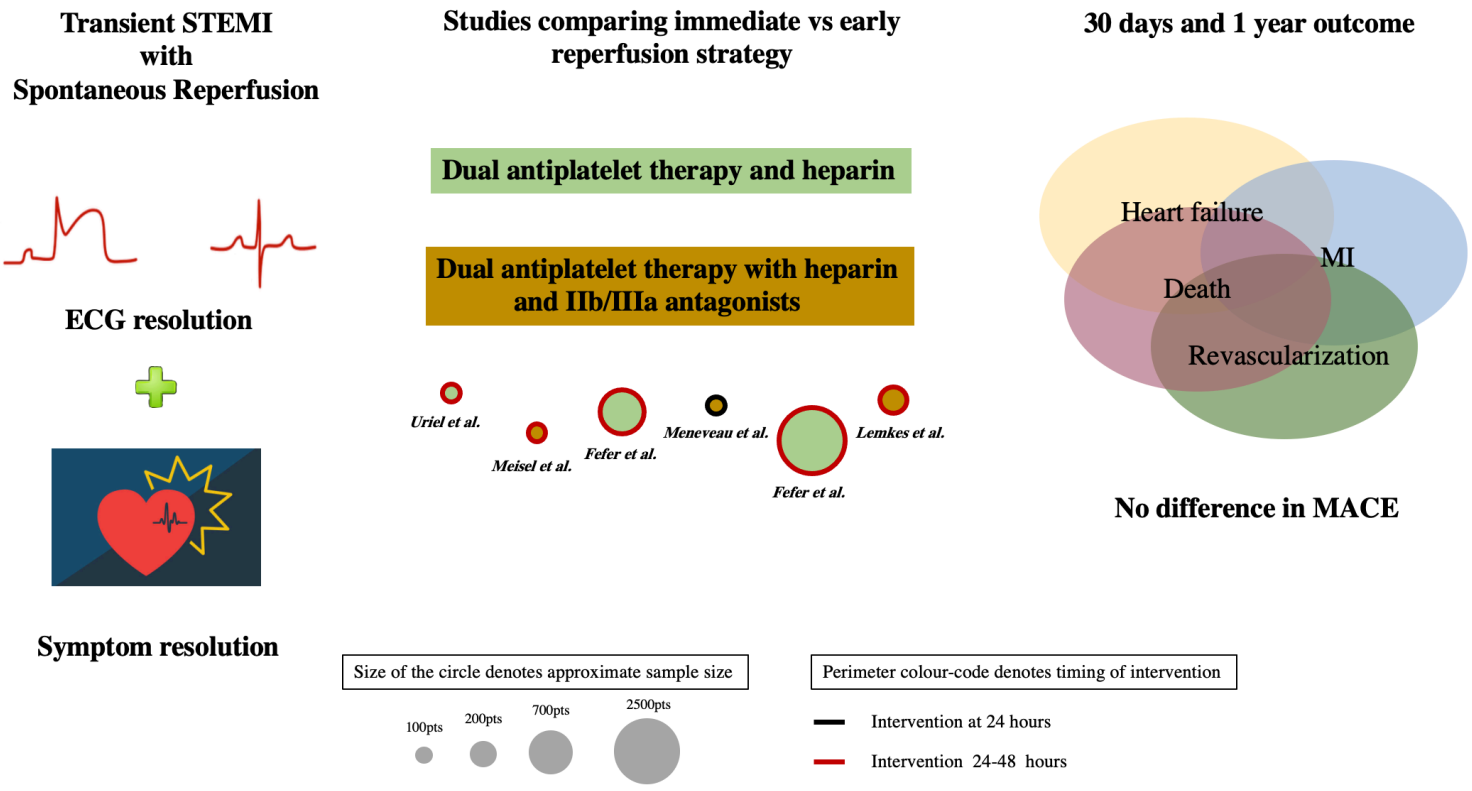
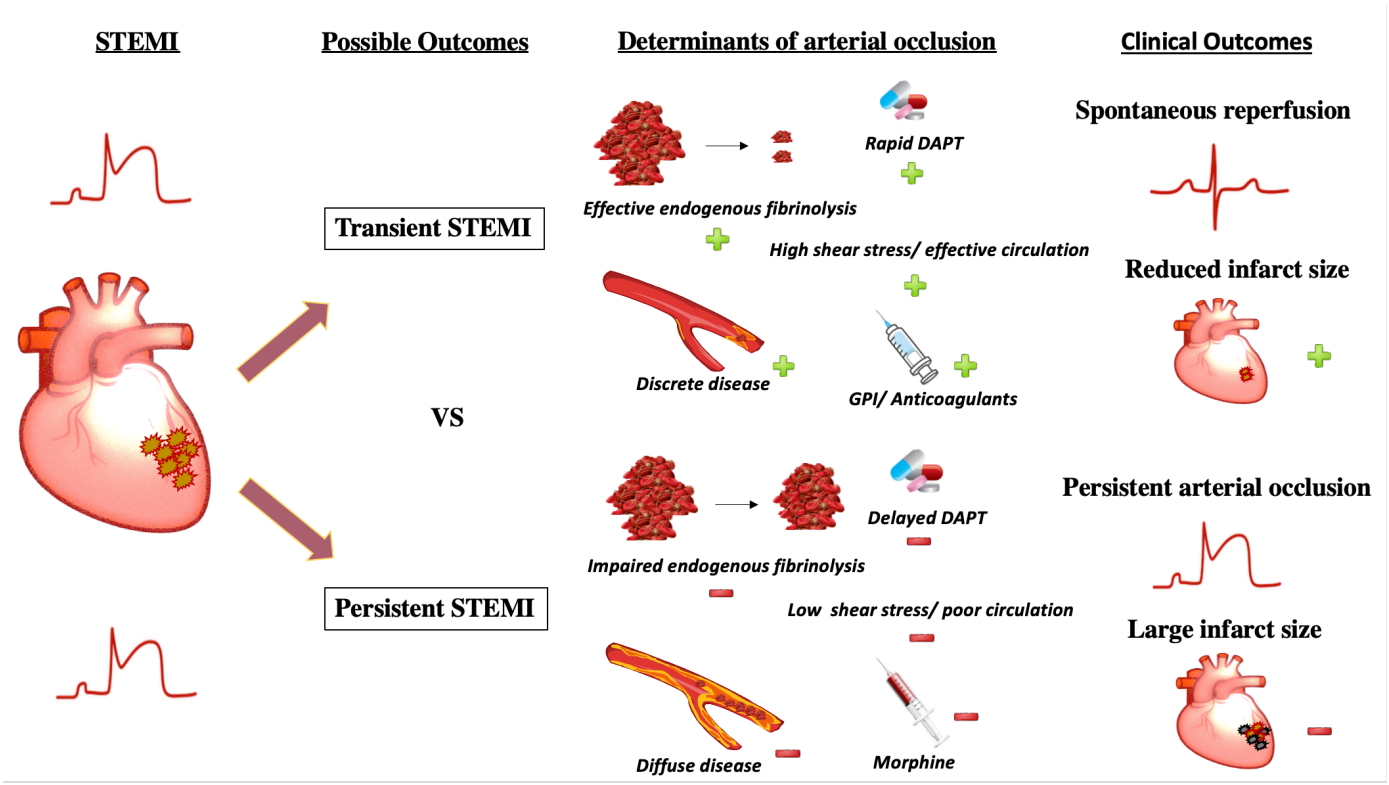
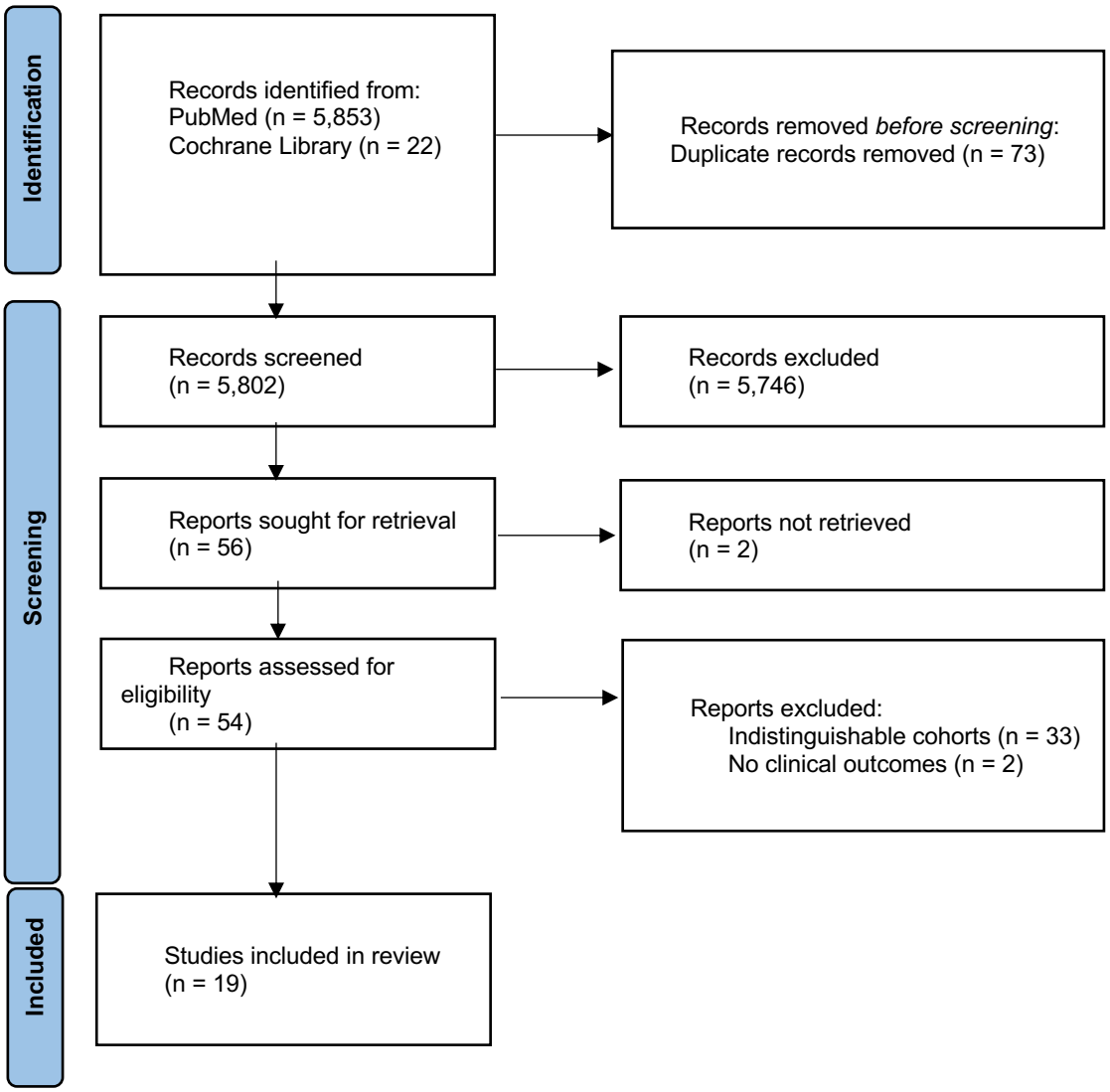


Figure 3 Central illustration. Determinants of arterial occlusion in STEMI



Supplemental Figure 1. Study flowchart



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• Author Declarations

O Ethics approval and consent to participate
Not applicable.

O Consent for publication
Not applicable.

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The authors confirm that the data supporting the findings of this study are available within the article.

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MF conceived the idea and wrote the first draft. MF, MP, NS and YG did the literature search and data interpretation. ME and DAG contributed to critical analysis. All authors discussed the results and contributed to the final manuscript.

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