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BCS Editorial

PCI in late-presenting STEMI: how late is too late?

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Take Home Messages

- PPCI is of benefit in patients presenting more than 12 hours post STEMI with evidence of ongoing ischaemia, shock, malignant arrhythmias, or heart failure
- PCI in patients presenting between 12 and 48 hours appears to reduce overall mortality, and improve LV function
- PCI in asymptomatic patients with an occluded infarct-related artery beyond 48 hours is not of benefit in the absence of significant angina or inducible ischaemia

Introduction

Between one in five and one in ten STEMI patients present more than twelve hours from onset of chest pain (1), and are thus deemed 'late-presenters'. This topic is particularly relevant during the ongoing Covid-19 pandemic with pressurised healthcare systems and some patients reluctant to seek medical attention. Late presenters are a challenging group to manage, and presentations vary considerably from those with ongoing chest pain and haemodynamic instability, to those who are asymptomatic. International management guidelines vary, and there is a relatively limited evidence base which is predominantly drawn from observational studies, of which two large new studies have been published this year. Ultimately, the key question is whether percutaneous coronary intervention (PCI) in these patients improves left ventricular (LV) function, and reduces mortality and morbidity.

This editorial will discuss the reasons for late presentation, give an overview of guidelines, and a review of the evidence in order to help guide decision-making for this varied cohort of patients.

The twelve hour cut off

'Late-presenters' are generally defined as patients presenting at greater than twelve hours from symptom onset, as it is recommended that reperfusion occurs within this time frame. This recommendation is extrapolated from animal studies and thrombolytic trials through to the modern era of primary PCI. In the 1970s the duration of ischaemia was identified as directly related to infarct size during animal studies (2). Animal models in fact suggested myocardial viability for only six hours, but clinical trials then demonstrated a benefit from revascularisation by thrombolysis beyond this up to twelve hours (3, 4). This difference between animal and real-world data can be attributed to a number of protective factors, including incomplete or dynamic artery occlusion (5) and the presence of collaterals, whereas animal trials rely on complete ligation of a coronary artery.

About the author

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Underlying coronary artery disease and prior ischaemia also allow a degree of protective myocardial preconditioning (6). These factors can help explain the benefit of revascularisation beyond six hours.

Two imaging-based observational studies have examined the effect of PPCI on infarct size in late-presenters, one using myocardial perfusion scans (MPS) (7) and one cardiac MRI (CMR) (8). Both used the respective imaging modality either directly before or after PPCI, then again at one to three months. Patients presenting between 12 and 72 hours were found in both studies to have a larger final infarct size, reduced myocardial salvage index (expressed as a proportion of area at risk and final infarct size) and reduced LV ejection fraction when compared with patients presenting at <12 hours.

Characteristics of late-presenters

Late presentation can be due to patient and or system factors which both contribute to the total ischaemic time and significantly increased mortality (9, 10). Observational studies (1, 10) have shown that late-presenters tend more often to be older, female, and diabetic, with one study finding that atypical chest pain was an independent predictor of late arrival, whereas prior myocardial infarction (MI) or PCI appeared to be significantly less frequent in late-presenters. Minimising patient delay is dependent on public health messaging, such as British Heart Foundation (BHF) campaigns to raise awareness of the importance of calling 999 if patients develop chest pain, rather than waiting or attempting to contact other health services. A BHF audit performed in Northern Ireland found that only 14% of patients admitted with a myocardial infarction (MI) had called 999 within an hour of symptoms (11).

System delay is related to delay in pre-hospital medical care, late recognition of STEMI, and by stopping at non-PCI hospitals or departments. Addressing system delay in treatment of STEMI patients has focused on developing treatment networks, allowing rapid pre-hospital triage, bypassing of non-PCI hospitals, and transfer directly from the ambulance to catheterisation laboratories (9). Overall the proportion of STEMI patients presenting late does appear to have fallen over the last fifteen years (1).

During the Covid-19 pandemic however, an increased delay has been documented due to demand on healthcare services and public reluctance to attend for non-covid illnesses. A retrospective study (12) compared reperfusion of STEMI patients treated over a two month period in 2019 and the same period in 2020, and found a significant increase in total ischaemic time greater than twelve hours. As well as an overall reduction in primary PCI (PPCI) procedures, in-hospital mortality in STEMI patients also increased.

Current guidelines

The European Society of Cardiology (ESC) STEMI guidelines (9) are summarised in figure 1. They advise that patients presenting at more than twelve hours with ECG evidence or symptoms consistent with ongoing ischaemia, heart failure (HF), shock or malignant arrhythmias, should undergo a PPCI strategy regardless of time of presentation (class I recommendation). In patients with an ‘evolved’ STEMI - presenting 12-48hrs – routine PPCI should be considered in all patients (class IIa), and the guidelines specifically state that ‘the presence of a Q wave should not necessarily change the reperfusion strategy decision’.

For those presenting beyond 48 hours, the ESC advise that either angiography or a non-invasive test for presence of residual myocardial ischaemia/viability should be performed, but routine PCI of an occluded infarct-related artery is not recommended (class III). This is based on evidence from the Occluded Artery Trial (OAT) (13) which is discussed in more detail below. In this situation revascularisation can be considered in the presence of angina. Practically speaking, this may involve either exercise testing or non-invasive ischaemia testing prior to angiography to guide decision making in the catheterisation laboratory.

In contrast, the current American College of Cardiology Foundation/American Heart Association guidelines on management of STEMI (14), albeit from 2013, advise PPCI between twelve and 24 hours of onset only if clinical and/or ECG evidence of ongoing ischaemia (class IIa). They do recommend PPCI for patients with STEMI and cardiogenic shock or acute severe heart failure regardless of the time of onset of symptoms (class I).

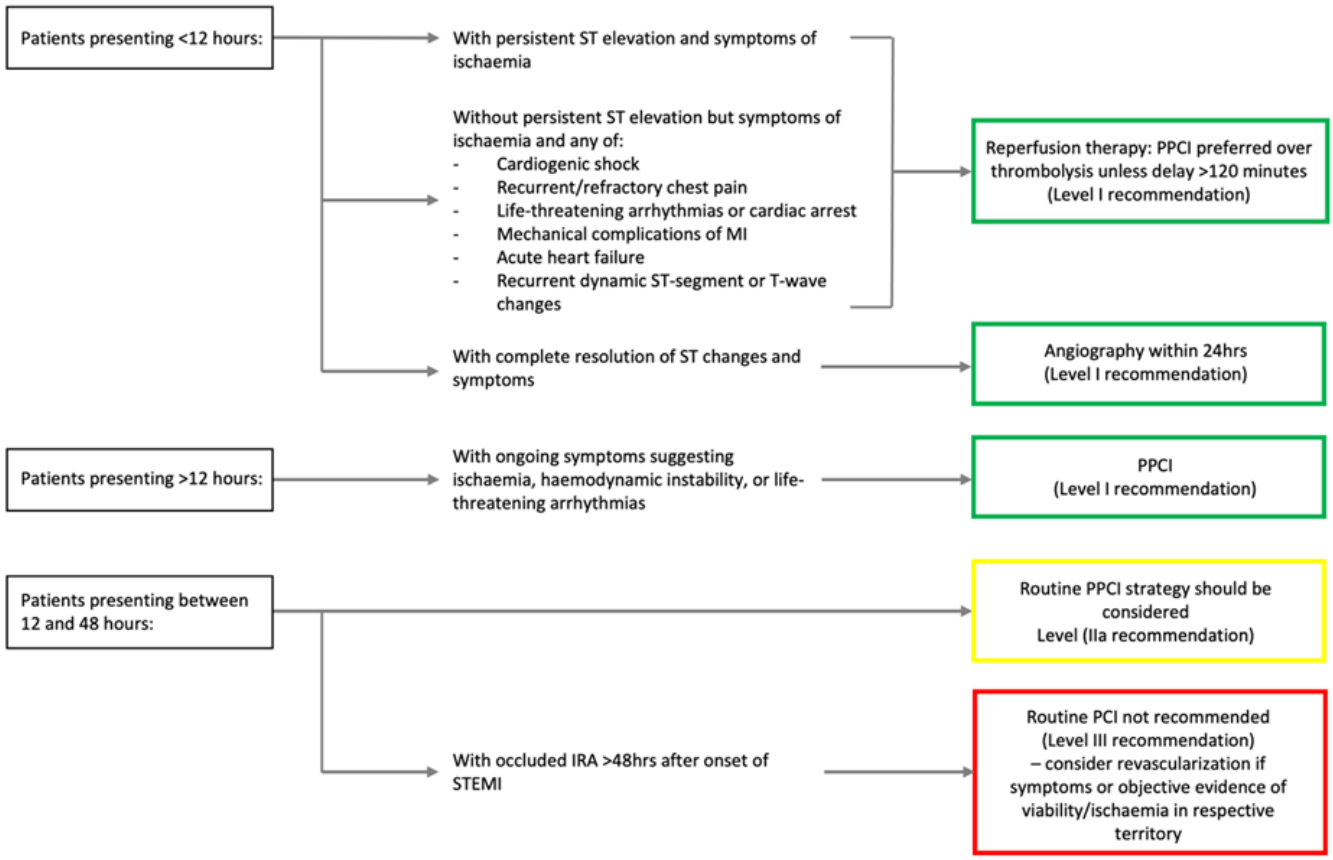

Figure 1. Summary of ESC STEMI guidelines based on time of presentation, adapted from (9). IRA, infarct related artery; PPCI, primary percutaneous coronary intervention

Current evidence

The evidence base for management of late-presenting STEMI patients is mixed and comprises two large recent observational studies, two imaging-based studies, and several randomised-controlled trials. However, the patient cohorts chosen are often very different in terms of clinical condition and timing of intervention. Below I have summarised the evidence for relevant questions in acute management.

How should we manage late-presenting STEMI patients with haemodynamic instability?

There are is a consensus across international guidelines that late-presenting STEMI patients with cardiogenic shock or acute HF should undergo PPCI, regardless of time of onset (9, 14). These reference a randomised trial (15) demonstrating that patients presenting with acute MI and cardiogenic shock had a reduced six month mortality when treated with emergency revascularisation rather than medical therapy (152 versus 150 patients, six month mortality 50.3% versus 63.1%, p=0.027). In addition, a registry study (16) of 36000 acute MI patients with HF indicating that in-hospital mortality in these patients was higher than those without HF (21.4% versus 7.2%, p<0.0005) and that on multivariate analysis PPCI conferred a survival benefit (OR 0.67). A summary of the relevant studies is included in **Table 1** below.

How should we manage late-presenting STEMI patients with ongoing ischaemia?

The ESC advise that in patients presenting >12 hours with ongoing ECG changes or symptoms of ischaemia, a PPCI strategy should be adopted up to 48 hours. However, American guidelines use 24 hours as a cut off for PPCI, citing two studies: the BRAVE-2 study (17) described below and an observational Polish study (18). A summary of relevant studies is listed in **Table 2** below.

Study	Type of study	Study population	Intervention	Endpoints	Results
Hochman *et al.* 1999 (15)	RCT	302 patients with shock due to LVF complicating MI	Randomised to emergency revascularisation (152 pts) or initial medical management (150 pts)	1° endpoint: all cause 30-day mortality 2° endpoint: six-month survival	Emergency revascularisation did not improved 30-day mortality but did improve six-month survival: 50.3% versus 63.1% (p=0.027)
Wu *et al.* 2002	Observational – registry-based	36303 patients with acute MI presenting with HF			In-hospital mortality (21.4% versus 7.2%, p<0.0005) and length of stay is higher in pts with HF than without

Table 1. Summary of studies looking at patients with acute MI and acute haemodynamic instability. *RCT = randomised controlled trial, LVF = left ventricular failure, MI = myocardial infarction, HF = heart failure*

Study	Type of study	Study population	Intervention	Endpoints	Results
BRAVE-2 – Schömig *et al*. 2005 (17)	RCT	365 stable pain-free patients presenting between 12 and 48 hours	Patients randomised to either conservative management (with symptom-guided ETT prior to discharge) or immediate invasive management	*1° endpoint:* Final LV infarct size measured on SPECT 5-10 days after randomisation *2° endpoint:* composite of death, recurrent MI and stroke at 30 days	Final LV infarct size significantly smaller in the invasive group. Secondary endpoint occurred in 4.4% patients in the invasive group and 6.6% in the conservative group, but not significant
Gierlotka *et al*. 2011 (18)	Observational study – registry-based	2036 STEMI patients presenting between 12 and 24hrs over a year from 2005 to 2006		12 month mortality	Of 2036 patients, 910 underwent an invasive approach and 92% underwent PCI – those who had invasive approach had lower 12 month mortality than those with a conservative approach: 9.3% vs 17.9% (p<0.0001)
Nepper-Christensen *et al.* 2018 (8)	Observational	865 STEMI patients included who all underwent PCI: 58 presenting between 12 and 72 hours of symptoms with ongoing ischaemia, and 807 patients presenting <12 hrs	All patients underwent CMR just after PCI and at 3 months	*Primary endpoint:* myocardial salvage index *Secondary endpoints:* final infarct size, presence of microvascular occlusion, LV function	Late-presenters had a smaller myocardial salvage index (0.58 vs 0.65, p=0.021), and larger final infarct size (p=0.037). Late presenters also had lower EF acutely and at 3 months (both p<0.001): at 3 months EF 51% vs 60%. Substantial salvage >50% seen in 65% late-presenters.

Table 2. Summary of studies looking at late-presenting STEMI patients with ongoing ischaemia.

Gierlotka et al. looked at 2036 STEMI patients presenting between 12 and 24hrs over a one year period between 2005 and 2006, of which 910 underwent an invasive approach and 92% of these underwent PCI. Those treated with an invasive approach had a significantly lower 12 month mortality than the conservatively managed group: 9.3% versus 17.9% Patients with haemodynamic instability were excluded, but it is not clear whether these patients did have ongoing ischaemia.

Nepper-Christensen et al. (8) who conducted a CMR study looking at the effects of PPCI on infarct size, specifically included patients only with ongoing signs of ischaemia. Although myocardial salvage was reduced compared to early presenters, overall duration of symptoms could not predict the effect of PPCI on myocardial salvage and therefore no specific time cut off could be identified. Notably in this study and in another imaging study (7), late-presenting patients still achieved substantial myocardial salvage: 65% and 41% patients respectively in each trial achieved myocardial salvage >50%.

Overall less trials have specifically looked at patients with ongoing chest pain. From observational data (10), mortality rates appear to be similar for those presenting between 12 and 24 hours, compared to those between 36 and 48 hours, supporting an equity of treatment for those presenting between 12 and 48 hours.

What is the role of PCI in late-presenting patients without ongoing ischaemia?

Where the ESC and American guidelines differ is in the management of those presenting at more than twelve hours without ongoing ischaemia, and there is no consensus as to the role of PCI in these patients. Studies have looked at patients within different time frames, and also with varying acuity of PCI. These are summarised below in **Table 3**.

The Beyond 12 Hours Reperfusion Alternative Evaluation 2 trial (BRAVE-2) (17) randomised 365 asymptomatic STEMI patients presenting between 12 and 48 hours to either conservative or invasive management, then assessed the effect of late revascularisation on infarct size five to ten days later using SPECT. The conservative group were treated with dual antiplatelets, unfractionated or low molecular weight heparin, and underwent a symptom-guided exercise tolerance test prior to discharge. Patients were switched to an invasive strategy if they had evidence of inducible ischaemia on exercise testing, or if they developed further anginal chest pain, haemodynamic instability, or serious arrhythmias; 8.7% of patients initially assigned to the conservative group underwent PCI by the time of the SPECT scan. Patients in the initial invasive group underwent angiography with PCI if appropriate immediately after arrival. The trial demonstrated a significantly reduced infarct size on SPECT in the PCI arm, with a mean difference of 6.8% between the groups. Although the secondary endpoint of a composite of death, recurrent MI and stroke at 30 days was more common in the conservative group (6.6% versus 4.4%), this was not statistically significant.

More recently, a Korean registry study (10) looking at 624 patients presenting between 12 and 48hrs of symptoms identified that a 'no primary PCI strategy' was significantly associated with an increased 180 day mortality: adjusted hazard ratio 1.82 ($p<0.001$). However it is not clear the characteristics of this patient group and whether they had ongoing ischaemia. Likewise, an observational study in France (1) looking at 1077 STEMI patients presenting between 12 and 48 hours during a one month period in 2005, 2010 and 2015, found that the all-cause death rate was lower among the 729 patients who were revascularized within 48 hours (at 2.1% versus 7.2%, $p<0.001$). At a median follow up of 58 months, the rate of all-cause death was 30.4 per thousand patient years in the revascularised group, versus 78.7 in the non-revascularised group ($P<0.001$). Again, it is not specified how many patients in the late-presenting group had symptoms of ongoing ischaemia.

Two trials specifically examine the role at recanalization of occluded infarct-related arteries in asymptomatic patients (13, 19). The larger OAT study (13) included over 2000 patients presenting between three and 28 days with an occluded infarct artery with LV ejection fraction <50% and/or proximal occlusion of a major epicardial vessel. The patients were randomised to optimal medical therapy with or without PCI within 24 hours. The primary composite end point of death, reinfarction, and NHYA class IV heart failure was more common in patients treated with PCI compared to medical management.

The authors speculate that this unexpected result may be due to loss of recruitable collateral flow thus predisposing patients who underwent PCI to infarct if spontaneous reocclusion occurs.

The DECOPI trial (19) likewise looked at 212 pain-free patients presenting with their first Q-wave MI and an occluded infarct-related vessel, who were randomised to PCI carried out between two and fifteen days (median eight days) or medical therapy. This was a low-risk patient group with the majority having single-vessel disease and only a third with LAD disease. There was no significant difference between the groups in the primary composite endpoint of cardiac death, heart failure and ventricular tachyarrhythmia.

The OAT and DECOPI trials seek to answer the same question but differ significantly in size and timing of PCI. These differences aside, together they do not demonstrate a benefit from PCI of an occluded infarct artery in asymptomatic late-presenters beyond 48 hours. A meta-analysis looking at late reperfusion in stable patients also supported this conclusion (20). Patients in this situation would be managed as for a chronic total occlusion (9).

Study	Type of study	Study population	Intervention	Endpoints	Results
BRAVE-2 – Schömig *et al*. 2005 (17)	RCT	365 stable pain-free patients presenting between 12 and 48 hours	Patients randomised to either conservative management (with symptom-guided ETT prior to discharge) or immediate invasive management	*1° endpoint:* Final LV infarct size measured on SPECT 5-10 days after randomisation *2° endpoint:* composite of death, recurrent MI and stroke at 30 days	Final LV infarct size significantly smaller in the invasive group. Secondary endpoint occurred in 4.4% patients in the invasive group and 6.6% in the conservative group, but not significant
Cho *et al.* 2021 (10)	Observational study – registry-based	5826 STEMI patients treated between 2011 and 2015, of which 624 presented late between 12 and 48hrs		180 and 3 year all-cause mortality	Late presenters had worse outcomes than those presenting <12hrs: 180 day mortality 10.7% vs 6.8%, 3 year mortality 16.2% vs 10.6% - both p<0.001. 'No primary PCI' strategy associated with increased 180 day mortality – adjusted hazard ratio 1.82 (p<0.001)
DECOPI – Steg *et al.* 2004 (19)	RCT	212 patients with first Q-wave MI and occluded IRA	Randomised after coronary angiography to either medical therapy or PCI performed 2-15 days after symptom onset.	Composite of cardiac death, non-fatal MI, and ventricular tachyarrhythmia	At mean 34 months follow up the primary endpoint was similar between the groups: 7.3% vs 8.7% (p=0.68). LV EF was 5% higher in the PCI group (p=0.013)
OAT – Hochman *et al.* 2006 (13)	RCT	2166 stable patients with total occlusion of infarct-related artery 3 to 28 days after MI, with either proximal occlusion or EF<50%	Randomised to either PCI with optimal medical therapy, or optimal medical therapy alone	Composite of death, reinfarction, or NYHA class IV HF	4 year primary outcome rate higher in the PCI group although not significant – 17.2% vs 15.6% (p=0.20). Rates of reinfarction were also higher in the LCI group – 7.0% vs 5.3% (p=0.13)

Table 3. Summary of studies looking at late-presenting STEMI patients without evidence of ongoing ischaemia.

Study	Type of study	Study population	Intervention	Endpoints	Results
Gierlotka *et al*. 2011 (18)	Observational study – registry-based	2036 STEMI patients presenting between 12 and 24hrs over a year from 2005 to 2006		12 month mortality	Of 2036 patients, 910 underwent an invasive approach and 92% underwent PCI – those who had invasive approach had lower 12 month mortality than those with a conservative approach: 9.3% vs 17.9% (p<0.0001)
Cho *et al.* 2021 (10)	Observational study – registry-based	5826 STEMI patients treated between 2011 and 2015, of which 624 presented late between 12 and 48hrs		180 and 3 year all-cause mortality	Late presenters had worse outcomes than those presenting <12hrs: 180 day mortality 10.7% vs 6.8%, 3 year mortality 16.2% vs 10.6% - both p<0.001. 'No primary PCI' strategy associated with increased 180 day mortality – adjusted hazard ratio 1.82 (p<0.001)
Bouisset *et al.* 2021 (1)	Observational study – registry-based	1077 latecomer STEMI patients (out of 6273 STEMI patients included in the registries) presenting between 12 and 48 hours)			729 latecomer patients (67.7%) were revascularised within 48hrs of admission. All-cause death rate was lower in the revascularized group at 30 days (2.1% versus 7.2%) and at median follow up of 58 months (both p<0.001). Multivariate analysis found revascularisation independently associated with significant mortality reduction (P=0.001)
Ndrepepa *et al.* 2009	RCT	365 stable pain-free patients presenting between 12 and 48 hours	Patients randomised to either conservative management (with symptom-guided ETT prior to discharge) or immediate invasive management	Four year mortality	321 patients completed four year follow up – mortality was higher in the conservative arm, 18.9% versus 11.1%, p=0.047

Figure 4. Summary of studies looking at the effect of PCI on mortality in late-presenting STEMI patients.

Does PCI in late-presenters affect mortality?

Data from a number of observational studies, one meta-analysis and follow up from one RCT, suggest that reperfusion by PPCI in late-presenters does reduce mortality. These studies are summarised in **Table 4**.

Gierlotka et al. (18) carried out a retrospective study of patients presenting between 12 and 24 hours (without haemodynamic instability) found that twelve month mortality was significantly reduced in those patients treated invasively compared to conservative management, as detailed above. A Korean study also found that a 'no primary PCI strategy' was associated with an increased mortality (10). Similarly, a large French observational study (1) found that the all-cause death rate amongst patients presenting between 12 and 48 hours was significantly lower in the revascularized latecomer group than the non-revascularised group at 2.1% versus 7.2%. The four year follow up of the BRAVE-2 study (21) also suggested reduced mortality in the PCI arm, although this was not statistically significant. A meta-analysis from 2008 (22) concluded that PCI of the infarct-related artery performed between 12 hours and 60 days after acute MI is associated with significant improvements in survival.

Does PCI in late-presenters affect LV function?

Overall data from imaging studies appear to indicate that reperfusion is associated with improved LV function (7, 8). The DECOPI trial (19) also found that LV ejection fraction was 5% higher in the PCI arm. These studies are summarised in **Table 5** below.

Study	Type of study	Study population	Intervention	Endpoints	Results
Busk *et al.* 2009 (7)	Observational	396 STEMI patients undergoing PPCI: 341 early presenters <12 hrs and 55 late presenters 12 – 72hrs	MPS performed before PCI and at 30 days	Final infarct size, salvage index (area at risk minus final infarct size, divided by area at risk), and LVEF	Late presenters had a large final infarct size (p=0.005), lower salvage index (p=0.05), and lower EF (48% vs 53%, p=0.04). Substantial salvage >50% seen in 41% late-presenters.
Nepper-Christensen *et al.* 2018 (8)	Observational	865 STEMI patients included who all underwent PCI: 58 presenting between 12 and 72 hours of symptoms with ongoing ischaemia, and 807 patients presenting <12 hrs	All patients underwent CMR just after PCI and at 3 months	*Primary endpoint:* myocardial salvage index *Secondary endpoints:* final infarct size, presence of microvascular occlusion, LV function	Late-presenters had a smaller myocardial salvage index (0.58 vs 0.65, p=0.021), and larger final infarct size (p=0.037). Late presenters also had lower EF acutely and at 3 months (both p<0.001): at 3 months EF 51% vs 60%. Substantial salvage >50% seen in 65% late-presenters.
DECOPI – Steg *et al.* 2004 (19)	RCT	212 patients with first Q-wave MI and occluded IRA	Randomised after coronary angiography to either medical therapy or PCI performed 2-15 days after symptom onset.	Composite of cardiac death, non-fatal MI, and ventricular tachyarrhythmia	At mean 34 months follow up the primary endpoint was similar between the groups: 7.3% vs 8.7% (p=0.68). LV EF was 5% higher in the PCI group (p=0.013)

Table 5. Summary of studies looking at the effect of PCI on LV function in late-presenting STEMI patients.

Conclusion

Late-presenting STEMI patients are a heterogenous group and this is reflected in a mixed evidence base. Evidence suggests that PCI offers a mortality benefit when performed up to 48 hours of symptom onset, with benefit demonstrated in asymptomatic patients as well as those with ongoing ischaemia or cardiogenic shock. Beyond 48 hours the recanalization of an occluded infarct related artery does not appear to be of benefit, and these patients would need to be managed on an individual basis. A key strategy in avoiding the morbidity and mortality associated with late presentation is public health promotion and ongoing service improvement to reduce total ischaemic time.

Disclosures

None

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