



Clinical research

Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutaneous coronary intervention

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KEYWORDS

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Aims The majority of patients with ST-elevation myocardial infarction (STEMI) are admitted to local hospitals without primary percutaneous coronary intervention (primary PCI) facilities. Acute transferral to an interventional centre is necessary to treat these patients with primary PCI. The present study assessed the reduction in treatment delay achieved by pre-hospital diagnosis and referral directly to an interventional centre.

Methods and results Two local hospitals without primary PCI facilities were serving the study region. Pre-hospital diagnoses were established with the use of telemedicine, by ambulance physicians, or by general practitioners. Primary PCI was accepted as the preferred reperfusion therapy in patients with STEMI. From 31 October 2002 to 31 January 2004 all patients transported by ambulance and transferred for primary PCI were registered. Patients with STEMI were divided into three groups: (A) patients diagnosed at a local hospital ($n = 55$), (B) patients diagnosed pre-hospitally and admitted to a local hospital ($n = 85$), and (C) patients diagnosed pre-hospitally and referred directly to the interventional centre ($n = 21$). When comparing group A with group B and C, no difference was found in age, sex, infarct location, or distance from the scene of event to the interventional centre, whereas the median time from ambulance call to first balloon inflation was 41 min shorter in group B compared with group A ($P < 0.001$) and 81 min shorter in group C compared with group A ($P < 0.001$).

Conclusion In a cohort of patients scheduled for admission to a local hospital and subsequent transferral to an interventional centre for primary PCI, those diagnosed pre-hospitally had shorter treatment delay compared with those diagnosed in hospital, both in the setting of initial admission to a local hospital, and to an even larger extent in the setting of referral directly to the interventional centre.

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Introduction

Primary percutaneous coronary intervention (primary PCI) has been established as the optimal reperfusion therapy in patients with ST-elevation myocardial infarction (STEMI),^{1,2} provided that the extra delay anticipated by a PCI strategy vs. immediate administration of a fibrin-specific thrombolytic agent (PCI-related delay) is less than 60 min.^{3,4} The time-window for primary PCI depends on the alternative thrombolytic treatment strategy feasible in the region of interest (pre-hospital or in-hospital initiation of treatment) as well as the treatment delay observed in the region. Even in urban areas and under optimal conditions pre-hospital thrombolysis may not be initiated until a median of 40–50 min after the ambulance call.^{5–8} Moreover, 60–90 min traditionally elapse from ambulance call until initiation of in-hospital thrombolysis.^{8–11} Thus, among ambulance-transported patients the acceptable delay from ambulance call to first balloon inflation may be 100–150 min. In patients initially admitted to hospitals without primary PCI facilities for diagnosis before transferral to an interventional centre (centre with primary PCI facilities) considerable delay exists at the local hospitals before departure (in-door-out-door time). In the latter patients, pre-hospital establishment of the diagnosis may reduce treatment delay and increase the proportion of patients being eligible for primary PCI within the accepted time-window. The purpose of this study was to assess and compare the treatment delay in three groups of patients suspected of STEMI, who were scheduled for admission to one of two local hospitals serving the study region and who were transferred to an interventional centre for primary PCI: (A) patients diagnosed at a local hospital, (B) patients diagnosed pre-hospitally and initially admitted to a local hospital, and (C) patients diagnosed pre-hospitally and referred directly to the interventional centre.

Methods

Study population

The study region consisted of 250 000 inhabitants. Two local hospitals without primary PCI facilities (Randers County Hospital and Silkeborg County Hospital, Denmark) served the study region. Prior to initiation of the study, agreement was reached among cardiologists in the region upon a DANAMI-2 (Danish Multicentre Randomized Study on Fibrinolytic Therapy vs. Acute Coronary Angioplasty in Acute Myocardial Infarction) approach¹ of transferring all patients with STEMI from the local hospitals to an interventional centre (Skejby University Hospital, Aarhus, Denmark) for primary PCI. The distance from the local hospitals to the interventional centre was 37 and 45 km, respectively. Pre-hospital diagnoses were established by ambulance physicians (physicians dispatched in emergency vehicles to the scene of the event), by general practitioners, or with the use of telemedicine. The latter strategy required patients to be transported by ambulances with telemedicine equipment (13 of 28 ambulances serving the region). In these patients, an electrocardiogram (ECG) was obtained on-scene

for subsequent transmission to the interventional centre. A physician on call evaluated the ECG, phoned the ambulance, interviewed the patient who was equipped with headphones, and established the pre-hospital diagnosis.¹²

From 31 October 2002 to 31 January 2004 all patients with STEMI transported by ambulance and transferred to the interventional centre for primary PCI were identified. Ambulance staff and physicians at the local hospitals identified patients prospectively by filling out standardized questionnaires. In addition, patient records were reviewed from all acute admissions to the interventional centre in order to identify patients not registered prospectively.

The diagnosis of STEMI required that significant ST-elevation (in two adjacent leads and ≥ 0.1 mV in leads I–III, aVF, aVL, V4–V6 and ≥ 0.2 mV in leads V1–V3)¹³ were present in a pre-hospital ECG or the first ECG obtained at the local hospital. Patients were excluded from the study if the physician responsible for the primary PCI procedure did not confirm the diagnosis of STEMI. Patients were also excluded if symptom duration was >12 h, if they were not transported by ambulance from the scene of event, or if they were unconscious on arrival at the local hospital or the interventional centre.

The remaining patients were stratified into three groups according to the pre-hospital diagnosis and referral strategy (Figure 1). (A) Patients diagnosed following admission to a local hospital. Adjunctive medication (i.e. aspirin, beta-blockers, nitroglycerin, diuretics, heparin, and clopidogrel) was initiated at the discretion of the local physician in charge. A physician accompanied the patient during the transferral for primary PCI. The catheterization laboratory at the interventional centre was alerted. (B) Patients in whom establishment of a pre-hospital diagnosis was attempted (i.e. a pre-hospital ECG was acquired) and if successful the local hospital was alerted prior to patient arrival. Patients otherwise followed the same strategy as group A patients. (C) Patients who were diagnosed pre-hospital and transferred directly to the interventional centre. This strategy was followed provided that a general practitioner or ambulance physician arrived on-scene and accompanied the patient during the transferral, or that transport time to the interventional centre was equal to or shorter than transport time to the local hospital. The catheterization laboratory was alerted prior to patient arrival. Heparin and clopidogrel were given on arrival at the interventional centre (not available in the ambulances).

Data collection

Ambulance personnel prospectively registered: time of ambulance call, arrival time at the scene of the event, departure time from the scene of the event, arrival time at the local hospital (group A and B patients only), departure time from the local hospital (group A and B patients only), and arrival time at the interventional centre. Time of first balloon inflation was registered at the catheterization laboratory. The following baseline and paraclinical data were registered from ambulance records and patient records: age, sex, time of symptom onset, episodes of ventricular fibrillation (at the scene of the event, during transport to the local hospital, at the local hospital, or during transferral to the interventional centre), sinus rhythm on admission (yes/no), heart rate on admission, infarct location (anterior if ST-elevation in at least two of the leads I, aVL, V1–V6 and non-anterior if ST-elevation in at least two of the leads II, III, aVF, V5–V6), cumulative ST-elevation,¹³ peak biochemical marker elevation within 3 days of admission [troponin-T, creatinine kinase myocardial band (CK-MB), and creatinine], ejection fraction (by echocardiography or ventriculography),

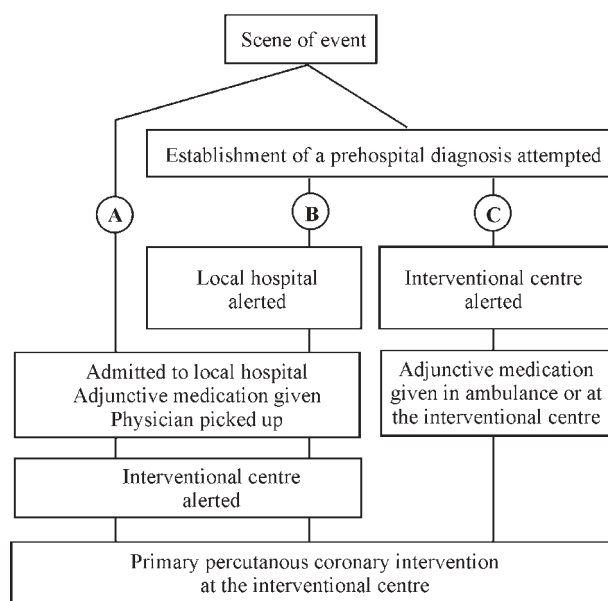


Figure 1 Strategies (A–C) of diagnosis and referral in STEMI patients scheduled for admission to local hospitals and transferred acutely to an interventional centre for primary PCI.

and time of discharge. Transport distance from the scene of the event to the local hospital and the interventional centre was calculated with the use of a web-based route planner.¹⁴

Statistics

Categorical variables are expressed as number (%), and continuous variables as median (25th–75th percentiles). The χ^2 test, Fisher's exact test, and the Mann–Whitney *U* test were used for pair-wise comparison of group A with group B, and group A with group C. The statistical significance level was $P < 0.05$ (two-sided test). The software package SPSS 10.0 was used for statistical analyses.

Results

A total of 184 consecutive patients suspected of STEMI with symptom duration of ≤ 12 h were transported by ambulance from the scene of the event and transferred from the study region to the interventional centre for primary PCI. At the catheterization laboratory the tentative diagnosis of STEMI was not confirmed in 23 (13%) patients (13 patients excluded from group B, and three excluded from group C). In the remaining 161 patients a diagnosis of STEMI was confirmed (55 patients in group A, 85 in group B, and 21 in group C). A pre-hospital diagnosis of STEMI was successfully established in 75 (88%) of group B patients, either by telemedicine ($n = 65$), by an ambulance physician ($n = 6$), or by a general practitioner ($n = 4$). The reasons for not establishing a pre-hospital diagnosis of STEMI in 10 patients were that: the ECG was not transmitted due to technically or geographically related transmission problems ($n = 4$), a pre-hospital ECG was acquired, however, the ambulance had no equipment

for ECG transmission ($n = 3$), the pre-hospital diagnosis with the use of telemedicine was non-ST-elevation myocardial infarction (NSTEMI) ($n = 1$), ST-elevation developed following ECG transmission ($n = 1$), or the physician at the interventional centre was unable to answer the call from the ambulance because he was held up by a serious case at the ward ($n = 1$). In 21 group C patients, a pre-hospital diagnosis of STEMI was established with the use of telemedicine ($n = 10$), by an ambulance physician ($n = 9$), or by a general practitioner ($n = 2$). No difference was found between groups in relation to age and sex (Table 1). Patients in group A had an intermediate distance to the local hospital when compared with group B and C patients, whereas no difference between groups was observed concerning transport distance to the interventional centre (Table 1). There was no difference between groups in the total number of patients experiencing ventricular fibrillation. However, the number of patients with ventricular fibrillation at the scene of the event was higher in group A compared with group B (Table 1). Group B and C patients had more pronounced cumulative ST-elevation compared with group A (Table 1). Four group A patients and three group B patients were not treated with primary PCI because it was not technically feasible. One additional group B patient was not treated with primary PCI due to spontaneous ST-resolution and only an insignificant coronary lesion at the coronary angiography (Table 2). When compared with group A, a significantly shorter time delay from ambulance call to first balloon inflation was observed in group B patients (168 vs. 127 min in group A vs. B, $P < 0.001$) and in group C patients (168 vs. 87 min in group A vs. C, $P < 0.001$) (Table 2 and Figure 2). The coronary biochemical marker elevation was higher in group C compared with group A, whereas no difference was found in ejection fraction or short-term mortality (Table 2).

Discussion

This study documents that a significant shorter delay before primary PCI is observed if patients are diagnosed pre-hospitally, especially if establishment of the diagnosis is followed by direct referral to an interventional centre.

The value of a pre-hospital diagnostic strategy is well established in the setting of thrombolysis,^{12,15–17} and when combined with pre-hospital thrombolysis associated with a 1-h reduction in treatment delay and 15–20 extra lives saved per 1000 treated.^{15,16,18,19} Very limited data exist concerning the beneficial effect of pre-hospital diagnosis in the setting of primary PCI. Wall and colleagues²⁰ demonstrated a significant reduction in door-to-balloon time (time from arrival at an interventional centre to first balloon inflation) in patients diagnosed pre-hospitally with the use of telemedicine compared with patients not diagnosed pre-hospitally (median door-to-balloon time 80 vs. 109 min, $P = 0.002$). However, their study was conducted among patients scheduled for admission directly to an interventional

Table 1 Characteristics of patients with STEMI transferred for primary PCI arranged according to strategy of diagnosis and referral

	No pre-hospital diagnosis. Initially admitted to a local hospital. Group A	Pre-hospital diagnosis. ^a Initially admitted to a local hospital. Group B		Pre-hospital diagnosis. ^a Referred directly to an interventional centre. Group C	
	n = 55	n = 85	P*	n = 21	P**
Age, years	60 (53–74)	67 (56–75)	0.22	63 (54–71)	0.73
Female sex	14 (27)	30 (35)	0.36	2 (10)	0.13
Distance, km					
On-scene to local hospital	12 (3–21)	5 (2–16)	0.017	20 (15–26)	0.012
On-scene to interventional centre	38 (36–47)	41 (36–48)	0.60	37 (31–51)	0.20
Ventricular fibrillation	5 (9)	2 (2)	0.11	1 (5)	1.00
At the scene of event	4 (7)	0 (0)	0.022	0 (0)	0.57
<i>En route</i> to the local hospital	0 (0)	1 (1)	1.00	–	–
At the local hospital	1 (2)	0 (0)	0.39	–	–
<i>En route</i> to interventional centre	0 (0)	1 (1)	1.00	1 (5)	0.28
ECG data on admission					
Sinus rhythm, %	46 (83)	78 (91)	0.25	16 (76)	0.72
Heart rate (per minute)	73 (57–92)	70 (59–85)	0.41	72 (55–98)	0.79
Anterior infarction, % ^b	23 (42)	34 (40)	0.86	7 (33)	0.60
Cumulative ST-elevation, mV	0.9 (0.7–1.8)	1.4 (0.9–2.3)	0.012	1.7 (1.4–3.0)	0.003

Categorical data are expressed as n (%) and continuous data as median values (25th–75th percentiles).

^aAttempts were made to establish a pre-hospital diagnosis.

^bST-elevation in ≥ 2 of the leads I, aVL, V1–V6.

*Group A compared with group B.

**Group A compared with group C.

centre. Among patients admitted directly to interventional centres without being diagnosed pre-hospitally, median door-to-balloon time was 93 min in DANAMI-2 and the EHS-ACS (European Heart Survey of Acute Coronary Syndromes),^{1,21} and as long as 185 min in NRM-4 (Fourth National Registry of Myocardial Infarction).²² In real life, the majority of patients with STEMI are admitted to hospitals without primary PCI facilities. Even in these patients, transferral for primary PCI is associated with improved patient outcome and recommended if PCI-related delay is less than 60 min.^{3,4} A major disadvantage in transferring patients from a local hospital to an interventional centre for primary PCI is the inherent delay at the local hospital before transferral, reported to be 50 and 73 min in DANAMI-2 and Air PAMI (Air Primary Angioplasty in Myocardial Infarction Study), respectively.^{1,23} In return, the interventional centre is alerted in time to prepare the catheterization laboratory staff prior to patient arrival, resulting in door-to-balloon time of only 25–30 min.^{1,23–25}

Given the long door-to-balloon time observed in patients admitted directly to interventional centres without being diagnosed pre-hospitally and the short door-to-balloon time observed in patients transferred from other hospitals, it may be speculated whether an optimal door-to-balloon time is achievable when implementing a strategy of pre-hospital diagnosis combined with transferral of patients directly to an interventional centre. In the present study only a 9-min longer door-to-balloon time was observed in patients diagnosed pre-hospitally and referred directly to the interventional

centre compared with patients initially admitted to a local hospital before transferral. Thus, in the present study, the median door-to-balloon time was considerably lower than previous findings in large-scale registries^{21,22} even among patients transferred directly to the interventional centre. This outlines the importance of an interventional centre that can be activated within short notice on a 24-h basis in order to take advantage of a strategy of pre-hospital referral.

The widespread implementation of a pre-hospital diagnostic strategy for patients with STEMI seems achievable with the use of telemedicine.^{12,17,26–29} We have previously demonstrated that, even in urban areas, up to 80% of ambulance-transported STEMI patients can be diagnosed pre-hospitally with the use of telemedicine.¹² In principle, such a strategy may be adapted in any region covered by a mobile phone network, and the physician responsible for the diagnosis can be located at a central centre serving a large catchment area. The optimal pre-hospital diagnostic strategy, though, may differ between regions according to local patient transportation and treatment logistics. However, it seems unrealistic to achieve widespread implementation of the strategies described in the ASSENT-3, CAPTIM, and other trials, in which 65–100% of ambulances included physicians in the crew.^{9,15,30–34} When considering the widespread implementation of a pre-hospital diagnostic strategy for patients with STEMI, alternatives other than telemedicine and ambulance physicians exist. Highly skilled ambulance nurses or paramedics can properly diagnose and treat patients with STEMI without

Table 2 Treatment delay and clinical outcome in patients with STEMI transferred for primary PCI arranged according to strategy of diagnosis and referral

	No pre-hospital diagnosis. Initially admitted to a local hospital. Group A	Pre-hospital diagnosis. ^a Initially admitted to a local hospital. Group B		Pre-hospital diagnosis. ^a Referred directly to an interventional centre. Group C	
	n = 55	n = 85	P*	n = 21	P**
Primary PCI performed	51 (93)	81 (95)	0.71	21 (100)	0.57
Time delay, min					
Symptom onset to ambulance call	88 (9-161)	44 (9-96)	0.22	28 (6-89)	0.22
Amb. call to amb. arrival on-scene	10 (8-15)	7 (5-12)	0.002	10 (6-11)	0.38
Amb. arrival on-scene to departure	13 (7-18)	13 (10-17)	0.55	21 (16-23)	0.003
Amb. call to local hospital arrival	47 (30-54)	31 (24-43)	0.004	—	—
Local hospital arrival to departure	55 (32-70)	35 (25-44)	0.046	—	—
Inter-hospital transport time	28 (23-30)	28 (25-35)	0.23	—	—
Amb. call to arr. at interventional centre	136 (106-165)	99 (81-122)	<0.001	57 (51-63)	<0.001
Door-to-balloon time	21 (17-31)	24 (20-33)	0.16	30 (26-38)	0.004
Amb. call to balloon inflation	168 (139-213)	127 (115-156)	<0.001	87 (82-102)	<0.001
Symptom onset to balloon inflation	250 (179-347)	175 (149-266)	0.002	129 (99-185)	<0.001
Ball. infl. within 120 min of amb. call	7 (13)	28 (33)	0.009	18 (86)	<0.001
Biochemical marker rise					
Peak troponin-T, µg/L	3.7 (0.9-7.4)	4.9 (2.1-8.6)	0.17	6.8 (3.8-11.6)	0.013
Peak CK-MB, µg/L	142 (63-349)	191 (71-359)	0.31	241 (152-486)	0.016
Peak creatinine, µmol/L	99 (87-115)	91 (77-107)	0.015	102 (84-127)	0.98
Ejection fraction	50 (43-55)	50 (40-55)	0.44	47 (36-55)	0.42
Hospital stay, days	5 (4-7)	5 (4-6)	0.69	6(4-7)	0.24
In-hospital deaths	6 (11)	4 (5)	0.19	0 (0)	0.18
Deaths within 6 months of discharge	0	0	—	0	—

Categorical data are expressed as n (%) and continuous data as median values (25th-75th percentiles).

^aAttempts were made to establish a pre-hospital diagnosis.

*Group A compared with group B.

**Group A compared with group C.

Amb, ambulance; arr., arrival; ball. infl., balloon inflation; Door-to-balloon time, arrival at the interventional centre to first balloon inflation; on-scene, at the scene of event; CK-MB, creatinine kinase myocardial band.

assistance from a physician.^{35,36} Computer algorithms for the diagnosis of STEMI may also be considered.^{11,37} The latter strategy, however, has previously been restricted to the diagnosis of 'large' STEMI with cumulated ST-elevation above 0.6-1.0 mV.^{6,38} Thus, to achieve widespread implementation of pre-hospital diagnosis in patients with STEMI, different strategies may be appropriate for different regions. Continuous evaluation and comparison of diagnostic accuracies of the different diagnostic algorithms, however, is necessary to ensure high diagnostic standards.

It may be speculated that primarily low-risk patients (limited ST-elevation) will be found eligible for pre-hospital referral directly to an interventional centre, hence patients with the *a priori* most favourable outcome.³⁹ On the contrary, we found that patients transferred directly to the interventional centre had the most pronounced ST-elevation and biochemical marker elevation, and a tendency towards shorter symptom duration, and were thus, the group of patients who were expected to gain most from early restoration of coronary patency.⁴⁰

Patients initially admitted to the local hospitals received similar medical treatment irrespective of

whether a pre-hospital diagnosis was established or not. However, this was not the case among patients referred directly to the interventional centre. The latter patients did not receive heparin or clopidogrel until arrival at the interventional centre, a fact potentially jeopardizing some of the expected benefit achieved by shortening the treatment delay before primary PCI.⁴¹ Thus, when adapting a future strategy of bypassing the nearest hospital and transferring patients with STEMI directly to interventional centres, ambulance staff should receive additional education in order to initiate relevant adjunctive medication (including heparin, clopidogrel, and glycoprotein IIb/IIIa inhibitors⁴²⁻⁴⁴) *en route*. Alternatively, a strategy of rendezvous may be considered, implying that centrally stationed ambulance physicians are dispatched to meet the patients *en route* to the interventional centre.

In some regions, strategies of pre-hospital thrombolysis may be as effective as transferral to interventional centres for primary PCI.³⁴ In Denmark, however, ambulance staff are not trained to treat patients with thrombolysis, and a DANAMI-2 approach of transferring patients with STEMI to primary PCI is accepted as the optimal treatment strategy in most regions.¹

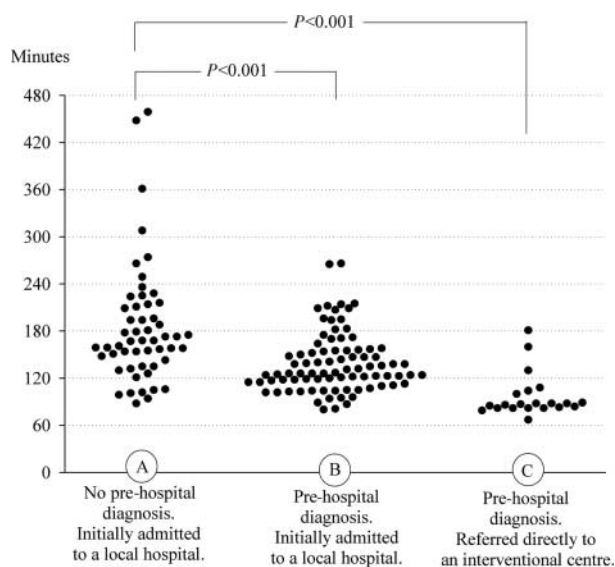


Figure 2 Time from ambulance call to primary PCI in STEMI patients scheduled for admission to a local hospital and transferred to an interventional centre, arranged according to strategy of diagnosis and referral.

Nonetheless, there must be a geographical border, at a certain distance or transport time from the interventional centres, beyond which patients may achieve a beneficial effect of pre-hospital thrombolysis or even in-hospital thrombolysis. In such regions transferral to primary PCI would result in a substantial PCI-related delay. In the future, thrombolysis followed by immediate transferral to primary PCI (facilitated PCI) may even prove beneficial for the latter patients.⁴⁵

Study limitations

To assess the reduction in treatment delay achieved when implementing a pre-hospital diagnostic strategy for the diagnosis of patients with STEMI, a randomized design would have been optimal; however, this was not allowed for ethical reasons. Irrespective of the study design, one should be careful when extrapolating the present findings to other regions. However, the key element in today's treatment delay for the majority of patients treated with primary PCI seems to be the delay at the local hospitals before acute transferral to an interventional centre. This delay is consistently reported to be ~1 h, comparable to the reduction in treatment delay achieved in the present study when bypassing the local hospitals. Thus, we expect similar reductions in treatment delay to be achievable in most regions introducing a pre-hospital diagnostic strategy followed by referral directly to an interventional centre. The present study was not statistically powered to evaluate mortality. Furthermore, any differences in mortality may be explained by selection bias. Finally, the trial was not powered to compare diagnostic accuracy for the different diagnostic strategies implemented in the study.

Perspectives

The present study indicates that, even in urban areas, pre-hospital diagnoses can be established successfully, which result in earlier initiation of primary PCI. Thus, a first step in reducing treatment delay may be the widespread implementation of pre-hospital diagnostic strategies. Future studies should evaluate whether a strategy of referral directly to an interventional centre, bypassing local hospitals, is feasible and safe, as well as study the beneficial effect of administration of adjunctive medication in the pre-hospital phase.

Conclusion

In a cohort of patients scheduled for admission to a local hospital and subsequent transferral to an interventional centre for primary PCI, those diagnosed pre-hospitally had shorter treatment delay compared with those diagnosed in hospital, both in the setting of initial admission to a local hospital, and to an even larger extent in the setting of referral directly to the interventional centre.

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