Urban and rural implementation of pre-hospital diagnosis and direct referral for primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction

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Aims	Primary percutaneous coronary intervention (PCI) is the preferred treatment for ST-elevation myocardial infarction (STEMI). The distance to primary PCI centres and the inherent time delay in delivering primary PCI, however, limit widespread use of this treatment. This study aimed to evaluate the impact of pre-hospital diagnosis on time from emergency medical services contact to balloon inflation (system delay) in an unselected cohort of patients with STEMI recruited from a large geographical area comprising both urban and rural districts.
Methods and results	From February 2004 until January 2007, data on pre-hospital timing and transport distance were prospectively recorded. Patients were divided into groups depending on achievement of pre-hospital diagnosis and/or direct referral to a primary PCI centre. Seven hundred and fifty-nine consecutive STEMI patients were included. In patients with a pre-hospital diagnosis and direct referral, the system delay was 92 vs. 153 min in patients without pre-hospital diagnosis ($P < 0.001$). Patients from rural areas were transported a median of 30 km longer than patients from urban areas; however, this prolonged the system delay by only 9 min.
Conclusion	Pre-hospital electrocardiographic (ECG) diagnosis and direct referral for primary PCI enables STEMI patients living far from a PCI centre to achieve a system delay comparable with patients living in close vicinity of a PCI centre.
Keywords	AMI • Angioplasty • Pre-hospital triage • Primary PCI • STEMI

Introduction

Rapid reperfusion therapy is the cornerstone of treatment for acute ST-elevation myocardial infarction (STEMI).[1,2] The sooner it can be instituted the better the outcome.[3] Mechanical reperfusion by primary percutaneous coronary intervention (primary PCI) is superior to fibrinolysis with respect to morbidity and mortality.[1,2,4,5] A major limitation to more widespread use of primary PCI is the delay from the first emergency medical services (EMS) contact to balloon inflation (system delay) due to a limited number of 24/7 PCI centres and long transport distances. Consequently, attempts

to optimize pre-hospital logistics and reduce system delay for STEMI patients are crucial.[6] Currently several initiatives worldwide addresses this challenge.[7–9] Numerous reports in highly selected patient populations have demonstrated that the implementation of pre-hospital electrocardiographic (ECG) diagnosis in STEMI reduces treatment delay.[10–15] This reduction is achieved by early activation of the catheterization laboratory and bypassing the local non-invasive hospital as well as the emergency room, the coronary care unit and the intensive care unit at the primary PCI centre.

The aims of the present study were (i) to describe the gradual implementation of pre-hospital ECG diagnosis of STEMI patients

in a county comprising both rural and urban areas and (ii) evaluate the impact of pre-hospital diagnosis on time from EMS contact to balloon inflation (system delay).

Methods

Geographical area

Aarhus County, Denmark (660 000 inhabitants, 4561 km^2) has one primary PCI centre (Aarhus University Hospital, Skejby) located in the outskirts of Aarhus City and three non-invasive referral hospitals.

The catchment area of the primary PCI centre has 100 000 patients and those of the three non-invasive hospitals have 200 000 (Aarhus City Hospital), 140 000 (Silkeborg Hospital), and 220 000 (Randers Hospital). The distance to the primary PCI centre is 4 km from Aarhus City Hospital and 47 and 37 km from Silkeborg and Randers Hospital. All patients referred from Silkeborg and Randers hospitals were considered to be living in a rural area while the urban area comprised patients from the catchment areas of Aarhus City Hospital and Aarhus University Hospital, Skejby. The longest transport distance from home to PCI centre was 100 km. Annually ∼350 STEMI patients in Aarhus County are treated with primary PCI.

Study population

From 2 February 2004 to 31 January 2007, 1049 consecutive patients from the study region were referred for primary PCI. Only patients transported from the scene of the event by the EMS ($n = 875$) were included in this study, as self-presenters ($n = 87$) or patients already admitted at a hospital when STEMI occurred ($n = 87$) were ineligible for pre-hospital diagnosis. Furthermore, patients with symptom duration ≥ 12 h ($n = 52$) and patients with bundle branch block ($n = 38$) were excluded, as these patients were not routinely referred directly for primary PCI during the entire study period. In 26 patients referred for primary PCI, the STEMI diagnosis was evidently wrong after catheterization. These patients were diagnosed with e.g. pericarditis, primary arrhythmia, or myocarditis. Thus, a total of 759 patients comprised the final study population. The ECG criteria for STEMI were: ST-elevation of ≥ 0.2 mV in leads V2 and V3 and 0.1 mV in all other leads or ST depression of 0.1 mV in V1−V4, with the ST changes being present in two contiguous leads.

Pre-hospital diagnosis

A pre-hospital diagnosis of STEMI was established either by general practitioners, ambulance physicians (onboard Mobile Emergency Care Units—MECUs), or by EMS paramedics utilizing telemedicine. The latter strategy implied that a 12-lead ECG was recorded using the LIFEPAK-12 defibrillator (Physio-Control, Inc., Redmond, WA, USA) and then transmitted wirelessly to the primary PCI centre via the global systems for mobile communications (GSM) network. The on-call cardiologist at the primary PCI centre interpreted the ECG and called the ambulance to conduct a short patient interview. If the ECG and the patient interview indicated STEMI, the ambulance was re-routed directly to the pre-alerted catheterization laboratory at the primary PCI centre. In case of patient transfer distances >20 km, the MECU was available for rendezvous, i.e. meeting the ambulance en-route to the primary PCI centre. This allowed advanced medical therapy and endotracheal intubation when necessary. Throughout the study period, four MECUs were available in the region.

Pre-hospital diagnosis by telemedicine, as described, was gradually implemented in Aarhus County from October 2002 to January 2006.

At the beginning of the study period in February 2004, 13 ambulances were equipped to transmit ECGs by telemedicine. During the following 12 months, the number increased to 28, and in January 2006 all 50 ambulances in Aarhus County were fully equipped.

Data collection

Pre-hospital patient data, transport data, and timing data were prospectively recorded by the EMS staff and the on-call cardiologists. Baseline patient characteristics and angiographic data were prospectively registered in a regional PCI database (Western Denmark Heart Registry) and in a local PCI chart at the primary PCI centre. Data on mortality were available from the Danish Central Office of Civil Registration providing daily updated vital status for all Danish Citizens. A censor date of 11 March 2010 was used. Data on cardiovascular death were provided by the Danish Cause of Death Registry. Cardiac death was defined as any death due to an evident cardiac cause, death related to PCI, unwitnessed death, and death from unknown causes.[16] In 21 patients, the Cause of Death Registry had incomplete recordings. In these patients, cause of death was acquired from the records of the individual patient's general practitioner. The study was approved by the Danish Data Protection Agency.

Statistics

Study patients were divided into three groups according to the diagnostic strategy and referral method. Group 1 comprised patients without pre-hospital diagnosis, therefore not eligible for direct referral to primary PCI. Group 2 comprised patients in whom a pre-hospital diagnosis was established, but without direct referral for primary PCI. Group 3 comprised patients with a pre-hospital diagnosis and direct referral to the primary PCI centre.

Dichotomous data are presented as numbers (percentage of valid cases). Percentages are rounded to two digits. Continuous variables are presented as medians (25−75th percentiles). The Fisher's exact test, χ^2 test, Mann−Whitney test, and Kruskall−Wallis test were used for comparison of categorical and continuous variables as appropriate. Mortality rates were summarized by construction of Kaplan−Meier plots and compared with log-rank statistics. Cox-regression analysis was used to evaluate the association between various covariates and long-term mortality. The statistical significance level was $P < 0.05$ (two-sided test).

Data were analysed using the PASW Statistics software package, version 18 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Groups 1, 2, and 3 comprised 216, 83, and 460 patients, respectively. All patients in group 1 were diagnosed by hospital physicians upon arrival at a local hospital. Pre-hospital diagnosis was performed in all patients in groups 2 and 3. Patients in group 2 were, however, not referred directly to primary PCI.

When comparing all three groups, patients in group 3 were younger with a higher proportion of males. In addition, they were more likely to receive glycoprotein IIb/IIIa inhibitors. Comparing groups 1 and 3, patients in group 3 were also younger ($P = 0.01$) with a higher proportion of males ($P = 0.01$) and were more likely to receive glycoprotein IIb/IIIa inhibitors ($P = 0.01$). Furthermore, they were also more likely to have one-vessel disease ($P = 0.05$) and better left ventricular ejection fraction ($P = 0.01$).

There were no further statistically significant differences in baseline characteristics between groups or between individual groups (*Table 1*).

Distance to primary percutaneous coronary intervention centre

For patients with a pre-hospital diagnosis referred directly to the primary PCI centre, the median distance was 10 km in urban areas vs. 40 km in rural areas. For patients without a pre-hospital diagnosis, the median distance was 10 km in urban areas vs. 55 km in rural areas.

Temporal trends in diagnosis and referral

Temporal changes in the method of diagnosis are presented in half-year intervals (*Figure 1*). During the first half-year of the study period, the diagnosis of STEMI was established by paramedics using telemedicine in 11% of the study cohort, whereas the proportion was 73% after complete telemedicine implementation in the area (*Figure 1*). The proportion of patients diagnosed by general practitioners remained unchanged throughout the study period, whereas the proportion diagnosed by the MECU decreased from 37 to 3%. A pre-hospital diagnosis was established

in 51% of the patients during the first half-year of the study when compared with 79% during the final half-year period.

There was a steady increase in the proportion of patients referred directly to the primary PCI centre over the course of the study. During the first half-year, 43% of the patients were referred directly to primary PCI, whereas in the last half-year this proportion had increased to 78%, ($P < 0.001$).

System delay in urban and rural areas

Timing data according to the geographical area and pre-hospital triage are displayed in *Table 2*. The proportion of patients meeting the guideline recommended EMS contact to balloon time limit of <120 min was 86% in patients with pre-hospital diagnosis and direct referral when compared with 32% in patients without pre-hospital diagnosis ($P < 0.001$).

In patients with a pre-hospital diagnosis, but no direct referral to the primary PCI centre, those from urban areas had a door-to-balloon time of 48 min when compared with 29 min for patients from rural areas ($P = 0.004$). In patients with a pre-hospital diagnosis and direct referral, the door-to-balloon time for urban patients was 35 vs. 32 min for rural patients ($P = 0.02$).

The system delay was investigated for each of the three groups according to the location of the local hospital, i.e. either in an urban or rural area (*Figure 2*). Median system delay was slightly

Table 1 Patient characteristics for the three groups

	Group 1—No pre-hospital diagnosis (n = 216)	Group 2—Pre-hospital diagnosis, no direct referral (n = 83)	Group 3—Pre-hospital diagnosis and direct referral (n = 460)	P-value
Pre-hospital patient characteristics				
Age at admission (years)	67 (57−79)	66 (58−74)	63 (56−73)	0.04
Male sex, n (%)	149 (69)	59 (71)	358 (78)	0.04
Killip class 3 or 4 at admission, n (%)	12 (6)	5 (6)	24 (5)	0.95
Anterior MI, n (%)	99 (46)	41 (49)	217 (47)	0.85
Smoking, n (%)	112 (56)	47 (58)	242 (55)	0.84
Diabetes mellitus[a], n (%)	22 (10)	8 (10)	37 (8.0)	0.64
Hypertension[a], n (%)	67 (32)	35 (42)	159 (35)	0.22
Hyperlipidaemia[a], n (%)	36 (18)	17 (22)	86 (19)	0.74
Prior MI, n (%)	20 (9.3)	10 (12)	48 (11)	0.77
In-hospital patient characteristics				
Patients with one-vessel disease, n (%)	99 (46)	44 (53)	248 (54)	0.29
PCI performed, n (%)	213 (99)	81 (99)	449 (98)	0.60
PCI with stent implantation, n (%)	201 (94)	76 (94)	447 (99)	0.48
Coronary artery bypass grafting, n (%)	3 (1.4)	2 (2.4)	13 (2.8)	0.52
Peak troponin-T value, ng/mL	3.9 (1.5−7.5)	2.7 (0.7−6.0)	3.2 (1.1−7.4)	0.18
Left ventricular ejection fraction (%)	50 (40−55)	50 (40−55)	50 (40−60)	0.04
Aspirin[b], n (%)	214 (99)	83 (100)	455 (99)	0.64
Unfractionated heparin[b], n (%)	212 (98)	83 (100)	452 (98)	0.47
Clopidogrel[b], n (%)	216 (100)	82 (99)	453 (99)	0.19
Glycoprotein IIb/IIIa[b], n (%)	164 (76)	68 (82)	387 (84)	0.04

Dichotomous data reported as number of cases and percentages in parenthesis. Continuous data are reported as medians (25−75th quartile). MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Patients in treatment at the time of admission.
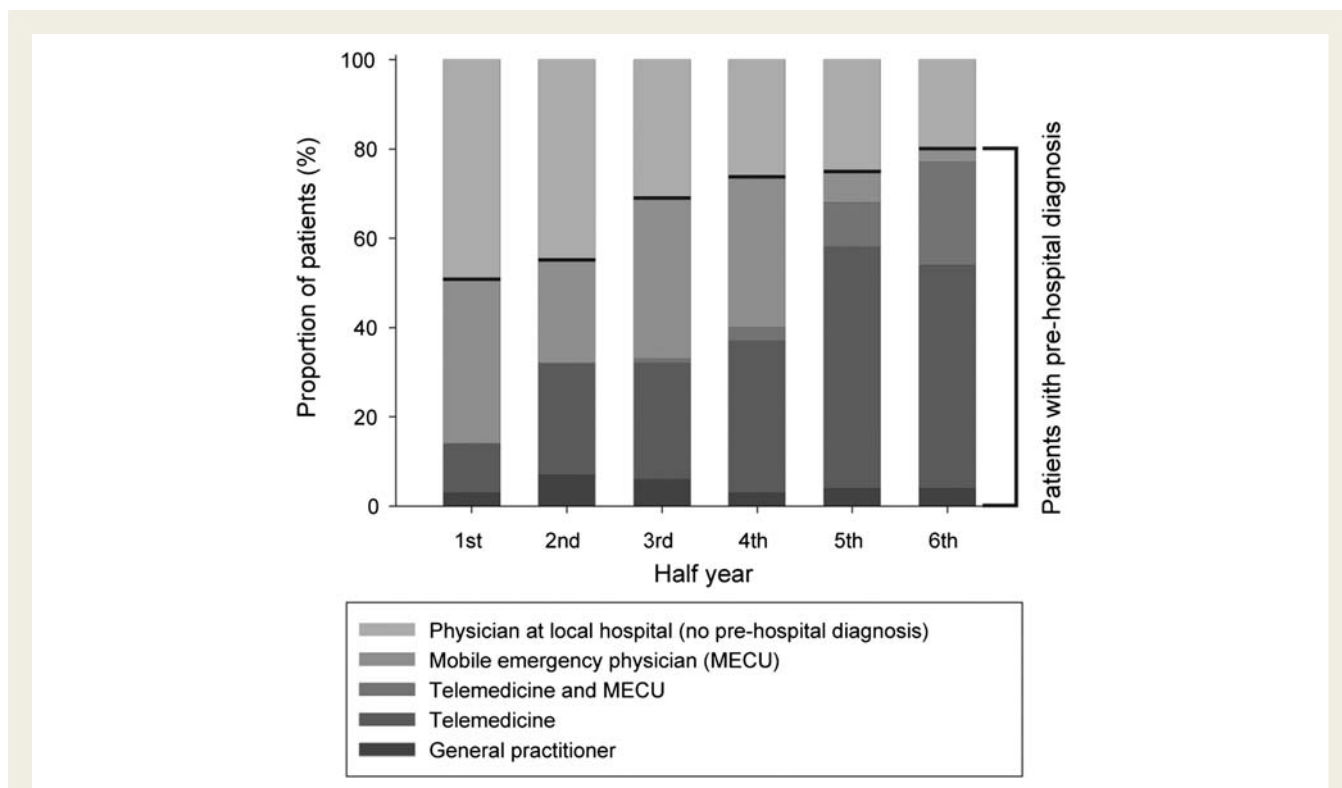[b]Within 24 h of admission.

Figure 1 Method used for ST-elevation myocardial infarction diagnosis. Distribution of diagnostic decision makers during half-year periods in the course of the study. Bold, horizontal lines mark the proportion of patients with pre-hospital diagnosis.

Table 2 Timing intervals in minutes according to referral method and geographic area

	Group 1—No pre-hospital diagnosis (n = 216)	Group 2—Pre-hospital diagnosis, no direct referral (n = 83)	Group 3—Pre-hospital diagnosis and direct referral (n = 460)	P-value
Symptom to balloon time	251 (175–346)	199 (156–270)	138 (105–204)	<0.001
Rural	259 (191–348)	215 (159–289)	151 (115–216)	
Urban	250 (166–331)	184 (133–230)	130 (97–189)	
EMS contact to balloon time	144 (112–186)	141 (109–179)	90 (77–107)	<0.001
Rural	167 (132–203)	152 (114–181)	93 (84–115)	
Urban	122 (97–156)	121 (98–153)	84 (72–102)	
Door-to-balloon time	30 (24–44)	31 (25–47)	34 (25–47)	0.02
Rural	29 (24–39)	29 (24–40)	32 (25–44)	
Urban	30 (24–47)	48 (29–89)	35 (26–51)	
EMS contact to balloon time ≤120 min, n (%)[a]	68 (32)	27 (33)	395 (86)	<0.001
Rural, n (%)	16 (15)	17 (28)	183 (83)	
Urban, n (%)	52 (48)	10 (46)	212 (89)	

Continuous data are reported as medians (25–75th quartile). EMS, emergency medical services.
[a]Valid cases (percentage of valid cases).

longer in directly referred patients diagnosed in rural when compared with urban areas, 93 vs. 84 min ($P < 0.001$).

The median system delay for patients referred directly to the primary PCI centre was 87 min in the first year of the study period when compared with 92 min in the last year of the study period ($P = 0.07$). For patients without pre-hospital diagnosis, the corresponding delay was initially 139 min and at the end of the study period, 153 min ($P = 0.26$). Thus, a significantly lower
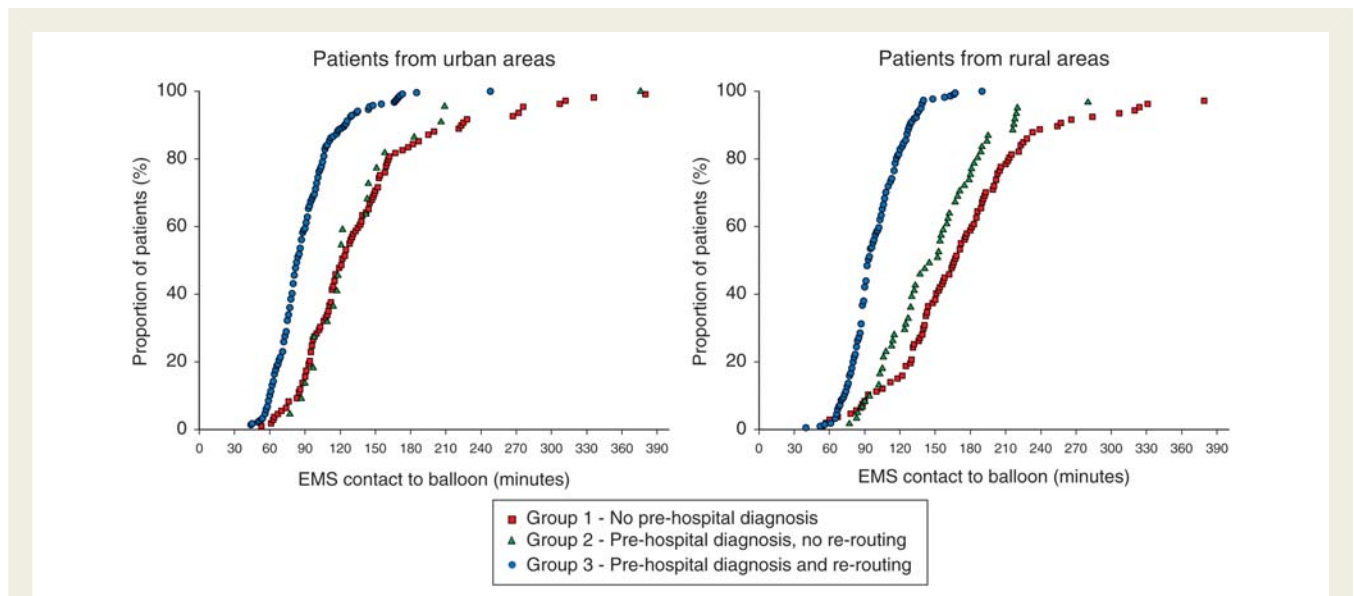
Figure 2 Time from emergency medical services (EMS) contact to balloon inflation according to geographical area.
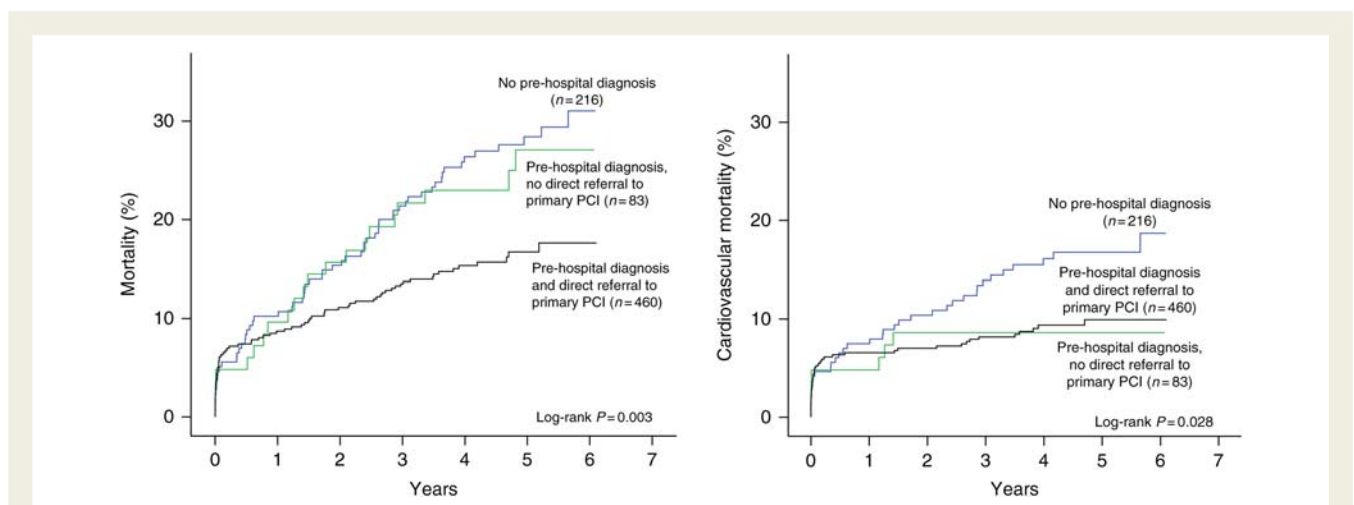

Figure 3 All-cause and cardiovascular mortality. Kaplan–Meier plot of all-cause and cardiovascular mortality according to method of diagnosis and referral. Primary PCI, primary percutaneous coronary intervention.

system delay of ~1 h was maintained throughout the 3 years between patients referred directly for primary PCI and patients initially transported to a local hospital without pre-hospital diagnosis ($P < 0.001$).

Long-term mortality

All-cause mortality with a median 4.3-year follow-up was significantly lower in patients with pre-hospital diagnosis and direct referral to a primary PCI centre compared with patients without pre-hospital diagnosis, 18 vs. 31% (log-rank $P = 0.003$, *Figure 3*).

In multivariable Cox-regression analysis, adjusting for all pre-hospital patient characteristics displayed in *Table 1*, pre-hospital diagnosis and direct referral to a primary PCI centre was associated with a hazard-ratio of 0.68 (95% CI 0.48; 0.96, $P = 0.028$).

A separate Kaplan–Meier estimate was performed for cardiovascular death. The difference in cardiovascular mortality between the three groups was again in favour for pre-hospital diagnosis and referral (log-rank $P = 0.028$, *Figure 3*), however, after adjusting for potential confounders the positive effect no longer reached statistical significance.

Discussion

The main findings of the present study are that pre-hospital diagnosis and direct referral for primary PCI: (i) can be successfully implemented in an entire region comprising both urban and rural areas, (ii) enables patients living far from a PCI centre to obtain

the same reduction in treatment delay as patients close to a PCI centre, and (iii) is associated with a reduction in long-term mortality.

A relatively high proportion of patients were referred directly to primary PCI initially in the study period (43%), which may be explained by the fact that telemedicine was already implemented in parts of the region.[13] Furthermore, an effective and dedicated pre-hospital MECU organization was already established in the area. In the beginning of the study period, the diagnosis of STEMI was based on telemedicine in only 11% of patients. Other patients were referred by emergency physicians or general practitioners at the scene of the event. The decrease in the proportion of patients diagnosed by emergency physicians throughout the study period was most likely caused by the gradual implementation of telemedicine. Consequently, the pre-hospital ECG was frequently recorded by the paramedics and diagnosed by the cardiologist at the PCI centre prior to the arrival of the MECU. Telemedicine was fully implemented in all ambulances by January 2006. At the end of the study period, complete regional coverage by telemedicine led to nearly a doubling in the proportion of patients being referred directly to primary PCI (78%).

Some patients were diagnosed in the ambulance, but were not directly referred for primary PCI (group 2). Sixty-two per cent of the patients from group 2 were included during the first year, when the concept of direct referral was still being introduced. Also, the patients in group 2 were mainly diagnosed at the scene by a GP or the MECU (65%), hence triaged solely at their discretion. The baseline characteristics of the latter patients were comparable with the other groups.

In the present study, the system delay in directly referred patients was slightly longer in patients from rural areas. However, the difference in median transportation distance of 30 km between groups resulted in a difference in system delay of only 9 min. Consequently, patients living in remote rural areas can be treated by experienced operators at high-volume primary PCI centres with negligible delay when compared with patients living in urban areas. Door-to-balloon times are shorter in primary PCI patients from rural when compared with urban areas. The latter reflects better preparatory conditions in the catheterization laboratory during longer transports, thus outweighing the potential disadvantage of living far from a primary PCI centre. Accordingly, we found that patients without direct referral to primary PCI have significantly shorter door-to-balloon times than patients referred directly. However, it is important to acknowledge the fact that the door-to-balloon time only constitutes a small part of the total system delay.

In this study, the reduction in treatment delay of up to 1 h as achieved by pre-hospital diagnosis and direct referral was sustained throughout the study period. In other words, the benefit of pre-hospital diagnosis in the real world is comparable with that achieved in previous focused clinical trials.[13]

National registries in Denmark provide complete information on mortality. Therefore, it was decided to perform a *post hoc* analysis on mortality data for patients with pre-hospital diagnosis and direct referral vs. patients without pre-hospital diagnosis.

Although small but potentially important differences in baseline characteristics were evident between study groups, we revealed a significant difference in long-term mortality favouring pre-hospital diagnosis and direct referral to a primary PCI centre. The difference remained significant in a Cox-regression model adjusted for all pre-hospital patient characteristics. However, when addressing cardiac death isolated, the lower mortality achieved by early diagnosis and referral was no longer statistically significant in the Cox-regression model. This finding most likely reflects residual confounding and thereby reveals the bias that is always inherent in observational studies. Although the lack of a statistically, significant mortality difference in cardiac death could also reflect the limited number of deaths from cardiovascular causes ($n = 84$). Given that the overall Health Care System Delay is associated with mortality, with a 10% increase in relative mortality per hour increase in System delay, it is expected that the reduction in system delay achieved by pre-hospital ECG and field-triage of patients will translate into a mortality reduction.[17]

The association between pre-hospital diagnosis and lower mortality found in this study lends further support to the trends and evidence for better outcomes with pre-hospital diagnosis and direct referral found in other studies.[14,15]

Limitations

Mortality data in our study should be interpreted cautiously, as the observational design allowed selection bias between groups regardless of adjustment in statistical models. Thus, residual confounding is impossible to eliminate. Data on heart rate at admission were not available in this study. This precluded e.g. the TIMI and Grace risk scores from being entered in the regression model. The only way to achieve reliable mortality data would be to randomize patients to a strategy of pre-hospital diagnosis and direct referral or not. Such a study is unethical in a community where the technology is already in use and physicians believe strongly in its efficacy.

Conclusion

Pre-hospital diagnosis of STEMI patients can be successfully implemented in a large geographical region covering both urban and rural districts. Pre-hospital ECG diagnosis and direct referral for primary PCI enable patients living far from a PCI centre to achieve a system delay comparable with that observed in patients near a PCI centre and may be associated with a lower mortality.

Author contribution

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