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Exploring variation in timely reperfusion treatment in ST-segment elevation myocardial infarction in Norway: a national register-based cohort study

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ABSTRACT

Objectives This study aimed to investigate determinants of reperfusion within recommended time limits (timely reperfusion) for ST-segment elevation myocardial infarction patients, exploring the impact of geography, patient characteristics and socio-economy.

Design National register-based cohort study.

Setting Multilevel logistic regression models were applied to examine the associations between timely reperfusion and residency in hospital referral areas and municipalities, patient characteristics, and socio-economy.

Participants 7607 Norwegian ST-segment elevation myocardial infarction patients registered in the Norwegian Registry of Myocardial Infarction during 2015–2018.

Main outcome measures The odds of timely reperfusion by primary percutaneous coronary intervention (PCI) or fibrinolysis.

Results Among 7607 ST-segment elevation myocardial infarction patients in Norway, 56% received timely reperfusion. The Norwegian goal is 85%. While 81% of the patients living in the Oslo hospital referral area received timely reperfusion, only 13% of the patients living in Finnmark did so.

Patients aged 75–84 years had lower odds of timely reperfusion than patients below 55 years of age (OR 0.73, 95% CI 0.61 to 0.87). Patients with moderate or high comorbidity had lower odds than patients without (OR 0.81, 95% CI 0.68 to 0.95 and OR 0.61, 95% CI 0.44 to 0.84). More than 2 hours from symptom onset to first medical contact gave lower odds than less than 30 min (OR 0.63, 95% CI 0.54 to 0.72). 1–2 hours of travel time to a PCI centre (OR 0.39, 95% CI 0.31 to 0.49) and more than 2 hours (OR 0.22, 95% CI 0.16 to 0.30) gave substantially lower odds than less than 1 hour of travel time.

Conclusions The varying proportion of patients receiving timely reperfusion across hospital referral areas implies inequity in fundamental healthcare services, not compatible with established Norwegian health policy. The importance of travel time to PCI centre points at the expanded use of prehospital pharmacoinvasive strategy to obtain the goals of timely reperfusion in Norway.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Almost complete data on the ST-segment elevation myocardial infarction patients in Norway during 2015–2018.
⇒ High-quality socioeconomic and administrative health service data at the individual level from national registers.
⇒ Many patients were transported by fixed-wing aircraft or helicopter, but only travel times by road were available for this study.
⇒ The study period 2015–2018 was some years ago. However, there has only been a moderate improvement in the proportion of patients receiving timely reperfusion in the years following.

INTRODUCTION

About 25% of acute myocardial infarctions are classified as ST-segment elevation myocardial infarctions (STEMI),[1] which in nearly all cases is due to a blockage of blood flow to the myocardium caused by an acute occlusion of a coronary artery. For patients suffering a STEMI, early diagnosis and immediate reperfusion are essential. Time elapsed before opening the artery influences myocardial salvage and the risk of cardiac arrest and death.[2 3]

The European Society of Cardiology (ESC) recommends primary percutaneous coronary intervention (pPCI) within 90 min from STEMI diagnosis for patients presenting in a PCI centre, and within 120 min for patients presenting in a non-PCI centre. Alternatively, when pPCI cannot be performed within 120 min, a pharmacoinvasive strategy is recommended if there are no contraindications. Following this strategy, fibrinolysis should be administered within 20 min from

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STEMI diagnosis, followed by coronary angiography (and PCI if indicated).[4] Based on these recommendations, the Norwegian Registry of Myocardial Infarction (NORMI) has developed national quality indicators measuring time to reperfusion treatment after first medical contact (FMC) for STEMI patients: pPCI should be conducted within 120 min, or alternatively, for patients who could not receive pPCI within this time limit, fibrinolysis should be administered within 30 min from FMC. No distinctions were made between patients presenting in a PCI centre, and patients presenting in a non-PCI centre.[5] Even though pPCI is recommended, several studies have shown that early fibrinolysis may produce earlier reperfusion and is efficient compared with delayed pPCI according to guidelines [2 6–8]

Studies from Europe, the Middle East and North Africa have shown regional variation in timely reperfusion treatment following STEMI.[9–11] Such variation has also been shown between countries[12] and within countries, especially between urban and rural areas.[13 14] Equal access to health services of high quality to the entire population, regardless of place of residence, gender, age, ethnicity and socioeconomic status is an overall and statutory health policy requirement in Norway, as stated in the Health Authorities and Health Trusts Act.

NORMI has established as a national goal that at least 85% of STEMI patients should receive timely reperfusion.[5] Over the last years, the NORMI indicator has shown that the Norwegian health service is far from achieving this goal, and that there is substantial geographic variation across areas concerning time to reperfusion. A study of time delay to reperfusion treatment has been conducted in the rural areas of Northern Norway.[15] Determinants of geographical variation in timely reperfusion treatment have not been investigated.

This study aimed to investigate variation in treatment quality by identifying determinants associated with timely reperfusion treatment after a STEMI. High-quality data from the National Medical Quality Register NORMI supplemented with information from other national registers, offered a unique opportunity to do so for the entire Norwegian STEMI population.

MATERIALS, METHODS AND STUDY POPULATION

Study design and data sources

The STEMI population of 8241 patients below 85 years of age, receiving reperfusion treatment within 12 hours from symptom onset to FMC registered during 2015–2018, was obtained from the NORMI. Patients with missing values were excluded according to figure 1, leaving 7607 patients in the study population.

Reporting to the NORMI, a medical quality register within the Norwegian Cardiovascular Disease Register, is mandatory for Norwegian hospitals. Informed patient consent is not required. The register contains clinical information and treatment quality indicators. Using an encrypted serial number derived from the unique

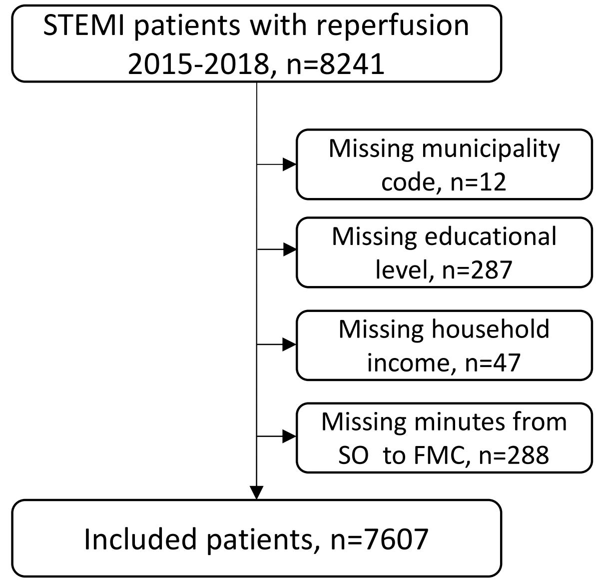

Figure 1 Patients with STEMI and reperfusion treatment, 2015–2018. FMC, first medical contact; STEMI, ST-segment elevation myocardial infarction. SO, symptom onset.

11-digit Norwegian national identity number, information concerning all specialised healthcare services provided for included patients during 2014–2018 was obtained from the Norwegian Patient Register (NPR), and individual demographic and socioeconomic data for the same period were obtained from Statistics Norway together with travel times.

Definitions

The outcome of this study was reperfusion treatment within recommended time limits (timely reperfusion) for STEMI patients, defined by the dichotomous NORMI quality indicator. As detailed above, the indicator does not differentiate between patients presenting in a PCI centre, and patients presenting in a non-PCI centre. It measures whether pPCI was conducted within 120 min, or alternatively, for patients who could not receive pPCI within this time limit, whether a pharmacoinvasive strategy using fibrinolysis was administered within 30 min from FMC.[5] STEMI patients were classified in accordance with the third universal definition of myocardial infarction.[16]

The patient's hospital referral area (HRA) was defined by place of residence (by municipality or city district codes) and grouped into the geographical areas served by the various Norwegian hospital trusts. Age was divided into four age groups: below 55 years, 55–64 years, 65–74 years and 75–84 years. Comorbidity was classified into none, medium (1–2 points) and high (≥3 points) based on information from the NPR and weights corresponding to an adjusted Charlson Comorbidity Index (PRI).[17]

Minutes from symptom onset to FMC include both patient and system delay since the types of delay were inseparable in our study. Minutes from symptom onset to FMC were grouped into ≤30 min, 31–120 min and ≥121 min.

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A tripartition of the original nine educational levels defined in the International Standard Classification of Education into lower, medium and higher education was done according to the Norwegian Standard Classification of Education.[18] The lower level corresponded to the compulsory school level in Norway, consisting of grades 1–10. Upper secondary school, either general theoretical education or vocational education and training, was defined as medium education. Both undergraduate and postgraduate university-level education were included in higher education.

Total after-tax income was obtained from Statistics Norway for each patient in the year prior to the year of infarction. To account for inflation, after-tax income was index adjusted to 2015 according to the Consumer Price Index. Income was allocated into four approximately equal sized income groups using quartiles: low (less than NOK 240 000), lower medium (NOK 240 000–NOK 310 000), higher medium (NOK 310 001–NOK 420 000) and high (more than NOK 420 000).

Travel time by road in minutes from the patient's municipality centre to the local hospital was calculated and grouped into three categories (≤20 min, 21–40 min and ≥41 min). Travel time to the nearest of the seven PCI centres in Norway in the time period 2015–2018 was computed similarly (≤60 min, 61–120 min and ≥121 min).

Statistical analyses

Data were analysed by using SAS V.9.4 (SAS Institute). The selection of determinants that could potentially influence timely reperfusion treatment was based on findings from previous studies.

This study used clustered data. Multilevel logistic regression models allow for the clustering of subjects within higher-level units when estimating the effect of both subject and cluster characteristics on subject outcomes.[19] Logistic multilevel regression analysis with three models was used to examine factors associated with timely reperfusion treatment.

First, a null model with cluster-specific random effects only (HRAs and municipalities nested within HRAs) was applied (model 1), detailing the proportion of the total individual variation that was attributable to the different levels in the model. This was relevant for obtaining correct estimates at the individual level, and for measuring the general effect of the higher levels.[19 20] The intraclass correlation coefficient (ICC) was calculated to measure variation at the HRA and municipality levels. The calculation of ICC is described in online supplemental file 1.

To assess whether the variation in the proportion who received timely reperfusion treatment was attributable to differences in individual characteristics, gender, age, comorbidity, minutes from symptom onset to FMC, educational level and income after tax was added in model 2. Potentially relevant interactions were assessed. The effect of minutes from symptom onset to FMC on the proportion who received timely reperfusion treatment was weakly interacting with gender (p=0.049, results not shown). Additional gender-stratified analysis was conducted and presented in online supplemental table S1. The two travel time variables were included in model 3 as higher-level variables to examine the specific contextual effects.

All models were examined for multicollinearity by inspecting correlation and variance inflation factors (results not shown). Study results were reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Patient and public involvement

The aim, scope and study design of this study were discussed in project meetings and dedicated meetings with appointed representatives from the Northern Norway regional health services user panel.

RESULTS

Descriptive statistics

During 2015–2018, a total of 7607 Norwegian patients received reperfusion for STEMI and were eligible for analysis. 56% of the 7607 patients (4268 patients) received reperfusion within recommended time limits (table 1). Median age of patients receiving timely reperfusion was 2 years lower than that of patients who did not receive timely treatment. Among patients aged <55 years, about 60% received timely reperfusion, compared with 49% among patients aged 75–84 years. Nearly 8 out of 10 patients were male and a larger proportion of males (57%) than females (52%) received timely reperfusion. Most patients had no comorbidity and 57% of them received timely reperfusion, in contrast with 48% of patients with high comorbidity (≥3 PRI points). When comparing time elapsed between symptom onset and FMC, 60% of patients with less than 30 min received timely reperfusion, while 48% of patients with more than 2 hours did so. The proportion receiving timely reperfusion treatment among the lower educated patients was 52%, compared with 62% among the highest educated patients. Likewise, there was an increase in the proportion of patients receiving timely reperfusion with increasing income, from 51% among patients with low income to 61% among patients with high income.

The proportion of patients with timely reperfusion varied substantially across the HRAs, ranging from 13% of patients living in Finnmark HRA, which serves the rural northern-most county in Norway, to 81% for patients living in Oslo HRA, serving major parts of the capital city (table 1, figure 2). The proportion receiving timely reperfusion treatment was higher among patients living within 20 min of their local hospital (62%) than among patients living more than 40 min away from their local hospital (34%). Similarly, a higher proportion of those living within 60 min of travel time from the nearest PCI centre (75%) received timely reperfusion than those living more than 2 hours away from the nearest PCI centre (26%).

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Table 1 Patient and area characteristics of STEMI MI patients in Norway 2015–2018, timely reperfusion treatment

	Timely reperfusion treatment		
	No	**Yes**	**Total**
No of patients	43.9% (3339)	56.1% (4268)	7607
Fibrinolysis	75.3% (934)	24.7% (307)	1241
Primary PCI<12 hours after FMC	34.0% (2038)	66.0% (3961)	5999
PCI>12 hours after FMC	100% (367)	0	367
Age			
Age at event, median (IQR)	65 (56–73)	63 (55–70)	64 (55–71)
Below 55 years	40.4% (709)	59.6% (1048)	1757
55–64 years	41.5% (938)	58.5% (1324)	2262
65–74 years	44.8% (1034)	55.2% (1274)	2308
75–84 years	51.4% (658)	48.6% (622)	1280
Gender			
Female	47.7% (824)	52.3% (904)	1728
Male	42.8% (2515)	57.2% (3364)	5879
Comorbidity			
No comorbidity	43.2% (2792)	56.8% (3677)	6469
Moderate comorbidity	47.2% (435)	52.8% (487)	922
High comorbidity	51.9% (112)	48.1% (104)	216
Minutes from symptom onset to FMC			
0–30 min	40.1% (862)	59.9% (1290)	2152
31–120 min	41.6% (1398)	58.4% (1966)	3364
121 min or more	51.6% (1079)	48.4% (1012)	2091
Educational level			
Lower	47.8% (1119)	52.2% (1223)	2342
Medium	43.8% (1663)	56.2% (2135)	3798
Higher	38.0% (557)	62.0% (910)	1467
Income after tax			
Low	49.3% (958)	50.7% (985)	1943
Lower medium	45.5% (877)	54.5% (1051)	1928
Higher medium	41.1% (755)	58.9% (1083)	1838
High	39.5% (749)	60.5% (1149)	1898
Hospital referral area			
Finnmark	86.6% (103)	13.4% (16)	119
University Hospital of North Norway	56.3% (174)	43.7% (135)	309
Nordland	82.6% (195)	17.4% (41)	236
Helgeland	78.2% (129)	21.8% (36)	165
Nord-Trøndelag	71.1% (155)	28.9% (63)	218
St. Olav	31.6% (148)	68.4% (321)	469
Møre og Romsdal	74.4% (293)	25.6% (101)	394
Førde	73.0% (119)	27.0% (44)	163
Bergen	27.6% (154)	72.4% (404)	558
Fonna	56.1% (137)	43.9% (107)	244
Stavanger	43.9% (208)	56.1% (266)	474
Østfold	36.6% (168)	63.4% (291)	459
Akershus	20.0% (155)	80.0% (619)	774

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Table 1 Continued

	Timely reperfusion treatment		
Innlandet	66.5% (553)	33.5% (279)	832
Vestre Viken	24.9% (154)	75.1% (464)	618
Vestfold	31.4% (132)	68.6% (289)	421
Telemark	53.4% (163)	46.6% (142)	305
Sørlandet	28.6% (118)	71.4% (295)	413
Oslo	18.6% (81)	81.4% (355)	436
Travel time to PCI centre			
0–60 min	25.4% (950)	74.6% (2793)	3743
61–120 min	51.1% (1064)	48.9% (1019)	2083
121 min or more	74.4% (1325)	25.6% (456)	1781
Travel time to local hospital			
0–20 min	38.5% (1924)	61.5% (3067)	4991
21–40 min	43.6% (597)	56.4% (773)	1370
41 min or more	65.7% (818)	34.3% (428)	1246

FMC, first medical contact; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Results from multivariable analysis

Variability within hierarchical levels

About 23% of the variation in receiving timely reperfusion treatment was due to differences between HRAs, while 4.7% was due to differences between municipalities, as shown in the results for ICC in model 1 (table 2).

Introducing individual characteristics in model 2 showed significantly different odds between some age groups, between patients without and with comorbidity, and between patients with less than half an hour and more than 2 hours from symptom onset to FMC. Inclusion of the individual characteristics in model 2 affected the ICC values only marginally.

When travel time to a local hospital and PCI centre was introduced in model 3, there was a substantial change in ICC. Variation due to differences between the HRAs was reduced from 23.1% in model 2 to 7.6% and variation due to differences between municipalities was reduced from 4.7% in model 2 to 2.7%. Hence, a substantial part of the differences between the HRAs was due to travel time to PCI centre (table 2, model 3).

Determinants associated with timely reperfusion treatment

The difference in the odds of receiving timely reperfusion for each HRA is depicted in figure 3 for models 1–3, with Akershus HRA as reference. The figure shows to what extent the three models accounted for the variation between the HRAs. In the random intercept model (model 1), all HRAs apart from Oslo HRA had significantly lower odds of timely reperfusion than Akershus HRA. When individual covariates were introduced in model 2, no substantial changes in the ORs occurred. The introduction of travel times in model 3 generally adjusted the ORs towards a smaller or no significant difference between Akershus and the other HRAs, as also indicated by the lowered ICC value. However, 10 HRAs still had significantly different odds than that of Akershus HRA.

In the fully adjusted model 3, there were no significant differences in odds of timely reperfusion for males and females (table 2). Increasing age reduced the chance of timely reperfusion (p=0.003 for linear trend). However, only patients in the age span of 75–84 years had significantly lower odds of timely reperfusion than patients below 55 years of age (table 2). This age effect was only statistically significant for males (p=0.002). For females, no significant age effect was found (online supplemental table 1).

In general, increasing comorbidity and time from symptom onset to FMC negatively influenced the odds of timely reperfusion (both with p value for linear trend <0.001). Patients waiting more than 1 hour from symptom onset to FMC had a 37% reduction in the odds of timely reperfusion compared with patients waiting less than half an hour (table 2), with no substantial differences between the genders (online supplemental table S1). Patients with moderate or high comorbidity had 19% and 39% lower odds of timely reperfusion than patients without comorbidity (table 2). The inverse relationship between comorbidity and odds of timely reperfusion was statistically significant in both genders (online supplemental table S1).

Travel time to PCI centre was the most influential determinant, as assessed with ORs, for timely reperfusion. Compared with those living less than 60 min from a PCI centre, patients living 61–120 min and more than 120 min away from a PCI centre had 61% and 78% lower odds of timely reperfusion, respectively

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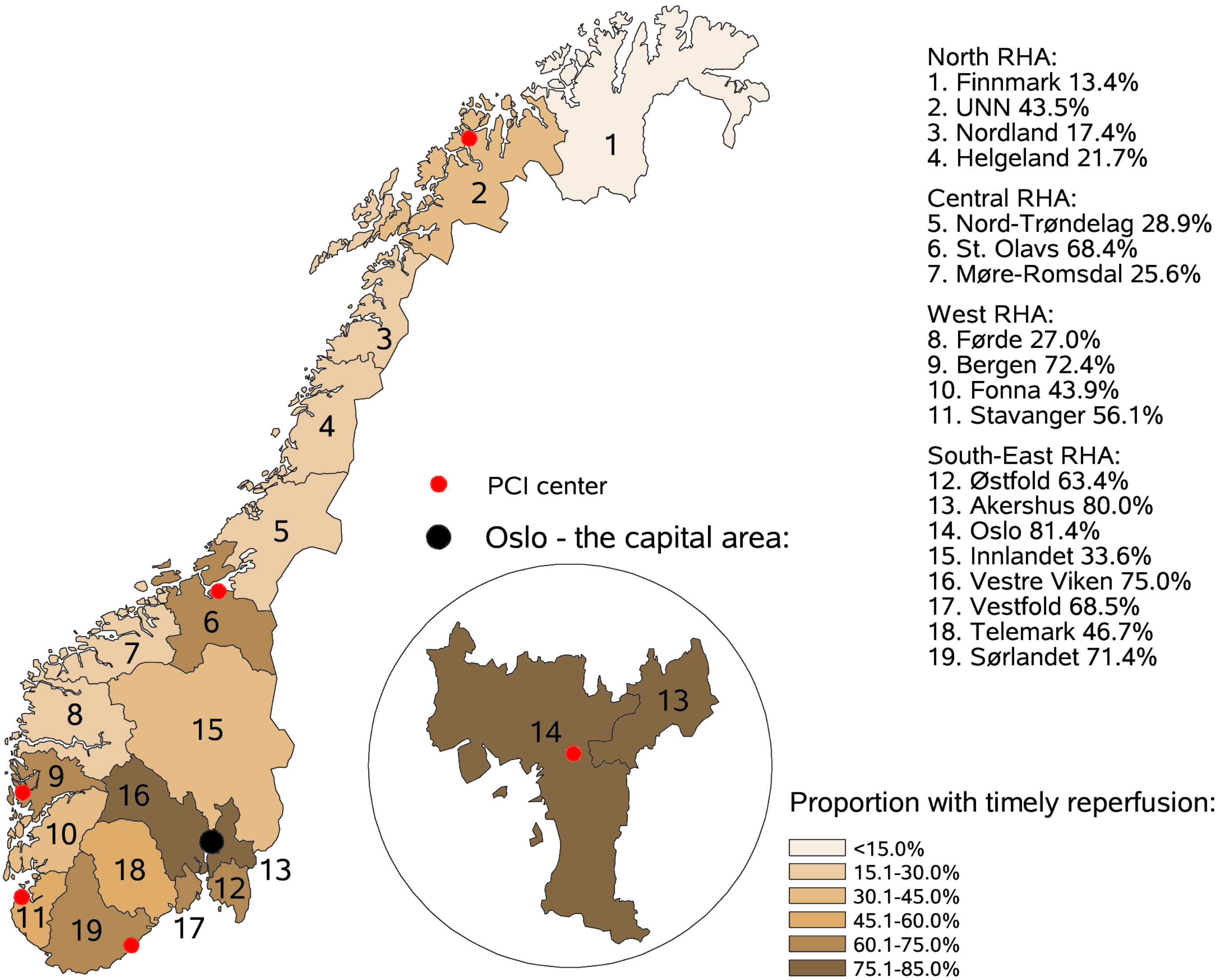

Figure 2 Proportion of patients receiving timely reperfusion treatment in the 19 hospital referral areas (HRAs) in Norway, 2015–2018. PCI centres marked with red dots. N=7607. PCI, percutaneous coronary intervention. RHA, regional health authority. UNN, University Hospital of North Norway.

(table 2). This effect was even stronger in females than in males (online supplemental table S1).

DISCUSSION

Principal finding

Only 56% of STEMI patients received reperfusion treatment within recommended time limits, which is not in line with established quality and equity goals in Norway. Travel time to PCI centre was the most important determinant for timely reperfusion treatment.

Age, comorbidity, gender and time delay

Myocardial infarction is one of the most important causes of death and disability in Norway. This highlights the importance of equitable high-quality health services for these patients. We found a substantial effect of age, where particularly male patients in the youngest age group were more likely to receive timely reperfusion treatment than male patients in the oldest age group. Atypical or delayed presentation, cognitive status, reluctance to use invasive or pharmacoinvasive treatment due to bleeding risk, frailty and even age discrimination are some potential explanations for why elderly patients had lower odds of timely reperfusion.[21] Contraindications were not examined in this study.

All patients included in the study were predefined candidates of timely reperfusion treatment by the NORMI. The goal is that at least 85% of the patients should be treated within the time limits, taking contraindications into account. Age is, however, not a valid priority criterion in Norway. Furthermore, it has been shown that time to pPCI is strongly associated with case fatality, especially in the oldest patients.[22]

Alongside high age, patients with moderate or high comorbidity had poorer odds of receiving timely reperfusion than patients without comorbidity, indicating that

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Table 2 Results from multilevel logistic regression for timely reperfusion treatment in STEMI MI patients in Norway 2015–2018

Model 1	Model 2	Model 3
	OR (95% CI)	**OR (95% CI)**
Individual covariates		
Gender		
Male	1.00 (ref.)	1.00 (ref.)
Female	0.90 (0.78 to 1.04)	0.89 (0.77 to 1.03)
P value	0.138	0.106
Age group		
Below 55 years	1.00 (ref.)	1.00 (ref.)
55–64 years	0.96 (0.83 to 1.11)	0.97 (0.84 to 1.12)
65–74 years	0.95 (0.82 to 1.11)	0.98 (0.84 to 1.13)
75–84 years	0.71 (0.60 to 0.85)	0.73 (0.61 to 0.87)
P value*	0.001	0.003
Comorbidity		
No comorbidity	1.00 (ref.)	1.00 (ref.)
Moderate comorbidity	0.82 (0.69 to 0.97)	0.81 (0.68 to 0.95)
High comorbidity	0.61 (0.44 to 0.84)	0.61 (0.44 to 0.84)
P value*	<0.001	<0.001
Minutes from symptom onset to FMC		
0–30 min	1.00 (ref.)	1.00 (ref.)
31–120 min	0.98 (0.86 to 1.12)	1.00 (0.88 to 1.14)
121 min or more	0.61 (0.53 to 0.71)	0.63 (0.54 to 0.72)
P value*	<0.001	<0.001
Educational level		
Lower	1.00 (ref.)	1.00 (ref.)
Medium	1.08 (0.95 to 1.23)	1.08 (0.95 to 1.23)
Higher	1.08 (0.91 to 1.27)	1.06 (0.90 to 1.26)
P value*	0.305	0.361
Income after tax		
Low	1.00 (ref.)	1.00 (ref.)
Lower medium	1.03 (0.88 to 1.20)	1.03 (0.88 to 1.19)
Higher medium	1.14 (0.97 to 1.35)	1.14 (0.97 to 1.34)
High	1.11 (0.93 to 1.32)	1.10 (0.93 to 1.31)
P value*	0.135	0.166
Area covariates		
Travel time to PCI centre		
0–60 min		1.00 (ref.)
61–120 min		0.39 (0.31 to 0.49)
121 min or more		0.22 (0.16 to 0.30)
P value*		<0.001
Travel time to local hospital		
0–20 min		1.00 (ref.)
21–40 min		0.98 (0.81 to 1.18)
41 min or more		0.93 (0.76 to 1.14)
P value*		0.460
Variance of random effects		

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Table 2 Continued

	Model 1	Model 2	Model 3
Residual variance			
Hospital referral area (HRA)	1.025	1.051	0.278
Municipality† HRA	0.215	0.214	0.097
ICC			
HRA	22.6%	23.1%	7.6%
Municipality† HRA	4.7%	4.7%	2.7%

Random intercept for HRA and municipality nested in HRA. N=7.607.
*P value for linear trend.
†Municipality level nested in HRA level.
FMC, first medical contact; ICC, intraclass correlation coefficient; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

frailty might be of importance. Reduced probability of reperfusion treatment among patients with comorbidity has been described in previous studies from Italy.[23 24] In line with our findings, these studies found that older and frail patients were excluded from reperfusion treatment, even when eligible. Acknowledging the ethical dimensions concerning treatment for the frailest patients, providing rapid treatment for these patients could still potentially be a goal for further quality improvement.

Previous studies have shown that female gender was associated with lower reperfusion rates and less guideline-recommended management.[25 26] In our study, we did not find a statistically significant gender effect.

HRA, travel time to PCI centre and the pharmacoinvasive strategy

The starting point of this study was to better understand the already known, and substantial, difference between HRAs in providing timely reperfusion for STEMI patients. Travel time to PCI centre explains a considerable part of the variation between HRAs for the majority of patients treated by pPCI. When this determinant was included in model 3, the ICC for HRA was reduced from 23.1% to 7.6% (table 2). Factors not included in this study, as differences in clinical practice and availability of cardiologists, may be of importance and should be explored further.

Travel time to PCI centre was the single factor that had largest impact on the odds of timely reperfusion. Acute STEMI patients living in rural areas of Norway are often transported to a PCI centre by helicopter or fixed-wing aircraft, reducing the actual travel time substantially and thereby enabling timely pPCI for a greater proportion of the patients. In the most rural northern parts of Norway, fixed-wing air ambulance flight time to the nearest PCI centre varies from 20 to 75 min.[15] However, the speed of air travel may cause time optimism regarding the use of pPCI as the preferred strategy. An overly optimistic assumption that in-hospital fibrinolysis or pPCI could be administered in a timely manner was frequently a cause of delays in Northern Norway in 2020–2021.[15] In the USA, only 17% of patients presenting in a non-PCI centre received pPCI in a timely manner during 2018–2021.[13]

Only 16% of the 7607 patients who received reperfusion in our study were treated with prehospital fibrinolysis. We believe this to be the main reason why travel time to PCI centre was so important. In Norway, where half of the patient population have more than 1 hour of travel time to a PCI centre, this is a remarkably low proportion. Pharmacoinvasive treatment has a risk of complications, especially in terms of intracranial bleeding.[2] Although the risk of intracranial bleeding after fibrinolysis is low, it has to be considered. This together with high age, comorbidity and other contraindications might explain why a pharmacoinvasive strategy was not used for some of these patients. However, the value and safety of this treatment strategy compared with delayed pPCI were documented in the STREAM trials, and by recent studies from Canada and Norway.[2 8 27 28] The risk of complications following pharmacoinvasive reperfusion can be reduced. Halving the dose of tenecteplase for elderly patients reduces the risk of intracranial haemorrhage[8 27 28] and is recommended for patients 75 years of age or older in the ESC guidelines.[4] The strategy of routine early PCI after fibrinolysis (within 6 hours) was associated to reduced risk of ischaemic complications compared with the standard strategy of performing a rescue PCI after failed fibrinolytic reperfusion[29] and may contribute to enhanced safety for patients receiving prehospital fibrinolysis.

In this study, only one of four patients who received pharmacoinvasive treatment did so within the recommended time limits. The explanations for this may be found at the system level. Bartnes *et al*[15] found that delayed establishment of a correct ECG diagnosis was the dominant cause of delayed fibrinolytic treatment. As in our study, they also found that a long time interval from symptom onset to FMC was an important obstacle, leaving some patients out of the 3-hour window where fibrinolysis has its best effect.[8] Such barriers may also explain some of the failures in obtaining timely reperfusion in this study.

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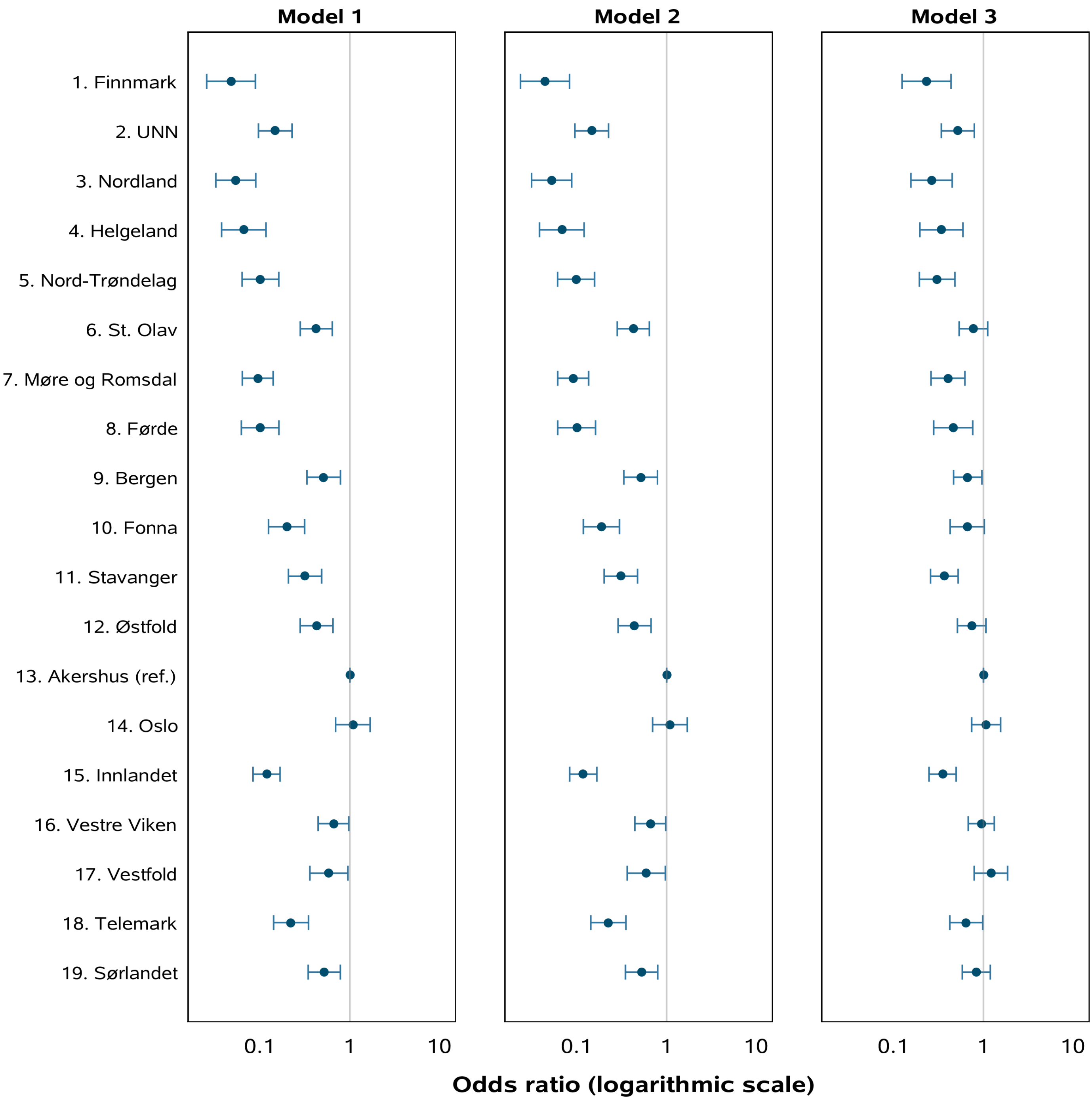

Figure 3 ORs with 95% CIs for hospital referral areas (HRAs) in Norway, 2015–2018, models 1–3. N=7607. UNN, University Hospital of North Norway.

Extended use of the pharmacoinvasive treatment strategy is the most promising way to improve patient outcome for STEMI patients living in rural areas of Norway. Recent results indicate that total ischaemic time, from symptom onset to reperfusion, is a more important prognostic indicator than time from FMC to reperfusion concerning infarct size and myocardial salvage. In this scenario, increased public awareness of STEMI symptoms and early medical system activation is important.[30] Extended use of pharmacoinvasive treatment is another possible strategy to reduce the total ischaemic time. Compared with regular in-hospital fibrinolysis, prehospital fibrinolysis with trained paramedics in the ambulances was associated with reduced time to reperfusion by almost 1 hour and reduced adjusted 1-year mortality by 30% in Swedish STEMI patients.[31] Pharmacoinvasive treatment may prevent 30 early deaths per 1000 STEMI patients treated within 6 hours after symptom onset, with largest absolute benefit among high-risk patients, including elderly patients.[4] Despite being feasible for about 75% of the patients, the use of prehospital fibrinolysis in the most rural areas of northern Norway was

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reduced from about 40% to 30% from 2006 to 2011[32] and was used for only 33% of the patients in 2020–2021.[15]

Strengths and limitations

The main strength of this study is the large sample size and good-quality data for STEMI patients in Norway, due to the high national coverage rate of nearly 90% for the study period in NORMI. Almost complete data on the study population combined with high-quality socioeconomic and administrative health service data represent an advantageous study design.

The register study design makes it difficult to draw causal conclusions on the associations found, as they to some extent may be confounded. Another limitation is the selection bias concerning the age of the quality indicator of timely reperfusion, which is the outcome of this study. The quality indicator only includes patients of less than 85 years of age, leaving out the oldest STEMI patients.

A substantial part of STEMI patients living in rural areas far from a PCI centre is transported by air. Because no information on flight times was available for this study, travel times by road were used to analyse the importance of living far from a local hospital and PCI centre. This inaccuracy is a weakness. However, the strong association between travel time to the nearest PCI centre and the probability of timely reperfusion may even have been strengthened if we had more exact measures of travel time.

The study period is 2015–2018, which was some years ago. However, in the years following, there has only been a moderate improvement in the proportion receiving timely reperfusion. In this study, 56% of STEMI patients were treated in a timely manner, whereas in 2022, this was the case for 64% of patients, still leaving Norway far from achieving the national goal of providing timely reperfusion for at least 85% of the patients (results at www.skde.no). The findings of this study may, therefore, be relevant also for patients treated after the study period.

Conclusion

The major differences in the proportion of STEMI patients receiving timely reperfusion across the HRAs imply that place of residence determines the quality of treatment the patients are likely to receive after a STEMI. The associations between age, comorbidity and minutes from symptom onset to FMC and timely reperfusion may offer insight into relevant areas for improvement in order to achieve established Norwegian health policy goals.

Eighty-four per cent of the STEMI patients who received reperfusion in Norway during 2015–2018 were treated by pPCI. We believe this was the main reason for why travel time to a PCI centre was the most influential determinant to timely reperfusion. Time optimism concerning pPCI as a preferred reperfusion strategy was likely an obstacle to ensure timely reperfusion for STEMI patients across Norway. Expanded use of the prehospital pharmacoinvasive treatment strategy in rural areas is important to obtain timely reperfusion in Norway. Further studies to better understand treatment delays and clinical outcome after delayed treatment are warranted.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but the study is based on secondary use of clinical and administrative register data. According to the Regional Committees for Medical and Health Research Ethics (REK), the study was not in the substantive scope of the Health Research Act and approval was not required (REK reference 2018/1955/REK nord). Exemption from the duty of confidentiality was granted by REK for data from NORMI and NPR, and by Statistics Norway for their data. The data controller has carried out a data protection impact assessment (DPIA). According to Norwegian law, further ethical approval or obtaining informed consent was not required for this study.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data underlying this article cannot be shared publicly due to legal restrictions. The original data were made available from the Norwegian Registry of Myocardial Infarction (NORMI), The Norwegian Patient Registry (NPR) and Statistics Norway under licence for the current study, and with an exemption from the duty of confidentiality for involved researchers (granted by The Regional Committees for Medical and Health Research Ethics (REK) for data from NORMI and NPR, and by Statistics Norway for their data). However, any researcher with approval of an exemption from professional secrecy requirements for the use of personal health data in research from the Regional Committee for Medical and Health Research Ethics (REK) would be able to create an almost identical (updated) dataset by applying to NPR, NORMI and Statistics Norway.

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REFERENCES

1 Jortveit J, Govatsmark RES, Digre TA, *et al*. Myocardial infarction in Norway in 2013. *Tidsskr Nor Laegeforen* 2014;134:1841–6.
2 Jortveit J, Pripp AH, Halvorsen S. Outcomes after delayed primary percutaneous coronary intervention vs. Pharmaco-invasive strategy in ST-segment elevation myocardial infarction in Norway. *Eur Heart J Cardiovasc Pharmacother* 2022;8:442–51.
3 Halle KK, Govatsmark RES, Bønaa KH. Treatment delay in STEMI is associated with heart failure and mortality. National Data from the Norwegian Myocardial Infarction Register.. *Eur Heart J* 2020;41.
4 Ibanez B, James S, Agewall S, *et al*. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J* 2018;39:119–77.
5 Govatsmark RES, Halle KK, Berge VB, *et al*. Årsrapport 2020 – Med plan for forbedringstiltak, . 2021Available: https://www.kvalitetsregistre.no/sites/default/files/2022-06/Norsk%20hjerteinfarktregister%20%C3%85rsrapport%202020%20nov21.pdf
6 Armstrong PW, Gershlick AH, Goldstein P, *et al*. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;368:1379–87.
7 Gershlick AH, Westerhout CM, Armstrong PW, *et al*. Impact of a Pharmacoinvasive strategy when delays to primary PCI are prolonged. *Heart* 2015;101:692–8.
8 Sinnaeve PR, Armstrong PW, Gershlick AH, *et al*. ST–segment-elevation myocardial infarction patients randomized to a Pharmaco-invasive strategy or primary percutaneous coronary intervention. *Circulation* 2014;130:1139–45.
9 Zeymer U, Ludman P, Danchin N, *et al*. Reperfusion therapies and in-hospital outcomes for ST-elevation myocardial infarction in Europe: the ACVC-EAPCI EORP STEMI Registry of the European society of cardiology. *Eur Heart J* 2021;42:4536–49.
10 Ludman P, Zeymer U, Danchin N. Care of patients with ST-elevation myocardial infarction: an international analysis of quality indicators in the acute coronary syndrome STEMI Registry of the Eurobservational research programme and ACVC and EAPCI associations of the European society of cardiology in 11 462 patients. *Eur Heart J Acute Cardiovasc Care* 2023;12:22–37.
11 Puymirat E, Battler A, Birkhead J, *et al*. Euro heart survey 2009 Snapshot: regional variations in presentation and management of patients with AMI in 47 countries. *Eur Heart J Acute Cardiovasc Care* 2013;2:359–70.
12 Cram P, Hatfield LA, Bakx P, *et al*. Variation in Revascularisation use and outcomes of patients in hospital with acute myocardial infarction across six high income countries: cross sectional cohort study. *BMJ* 2022;377:e069164.
13 Jollis JG, Granger CB, Zègre-Hemsey JK, *et al*. Treatment time and in-hospital mortality among patients with ST-segment elevation myocardial infarction, 2018-2021. *JAMA* 2022;328:2033–40.
14 Stopyra JP, Crowe RP, Snavely AC, *et al*. Prehospital time disparities for rural patients with suspected STEMI. *Prehosp Emerg Care* 2023;27:488–95.
15 Bartnes K, Albrigtsen H, Iversen JM, *et al*. The barriers to rapid reperfusion in acute ST-elevation myocardial infarction. *Cardiol Ther* 2022;11:559–74.
16 Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551–67.
17 Nilssen Y, Strand T-E, Wiik R, *et al*. Utilizing national patient-register data to control for Comorbidity in Prognostic studies. *Clin Epidemiol* 2014;6:395–404.
18 Barrabés N, Kjølstad GØ. Norwegian standard classification of education 2016. 2017. Available: https://www.ssb.no/en/utdanning/artikler-og-publikasjoner/norwegian-standard-classification-of-education-2016.
19 Austin PC, Merlo J. Intermediate and advanced topics in Multilevel logistic regression analysis. *Stat Med* 2017;36:3257–77.
20 Merlo J, Wagner P, Austin PC, *et al*. General and specific Contextual effects in Multilevel regression analyses and their paradoxical relationship: a conceptual Tutorial. *SSM Popul Health* 2018;5:33–7.
21 Turk J, Fourny M, Yayehd K, *et al*. Age-related differences in reperfusion therapy and outcomes for ST-segment elevation myocardial infarction. *J Am Geriatr Soc* 2018;66:1325–31.
22 Larsen AI, Loland KH, Hovland S. 226 patients from NORICA. *J Am Heart Assoc* 2022;11:e024849.
23 Balzi D, Barchielli A, Buiatti E, *et al*. Age and Comorbidity in acute myocardial infarction: a report from the AMI-Florence Italian Registry. *Am J Geriatr Cardiol* 2006;15:35–41.
24 Balzi D, Barchielli A, Santoro GM, *et al*. Management of acute myocardial infarction in the real world: a summary report from the AMI-Florence Italian Registry. *Intern Emerg Med* 2008;3:109–15.
25 Hellgren T, Blöndal M, Jortveit J, *et al*. 10 sex-related differences in the management and outcomes of patients 11 hospitalized with ST-elevation myocardial infarction: a comparison within 12 four European myocardial infarction registries. *Eur Heart J Open* 2022;2.
26 Johnston N, Bornefalk-Hermansson A, Schenck-Gustafsson K, *et al*. Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada? *Eur Heart J Acute Cardiovasc Care* 2013;2:350–8.
27 Van de Werf F, Ristić AD, Averkov OV, *et al*. STREAM-2: half-dose Tenecteplase or primary percutaneous coronary intervention in older patients with ST-segment-elevation myocardial infarction: A randomized, open-label trial. *Circulation* 2023;148:753–64.
28 Bainey KR, Armstrong PW, Zheng Y, *et al*. Pharmacoinvasive strategy versus primary percutaneous coronary intervention in ST-elevation myocardial infarction in clinical practice: insights from the vital heart response Registry. *Circ Cardiovasc Interv* 2019;12:e008059.
29 Cantor WJ, Fitchett D, Borgundvaag B, *et al*. Routine early Angioplasty after Fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009;360:2705–18.
30 Redfors B, Mohebi R, Giustino G, *et al*. Time delay, infarct size, and Microvascular obstruction after primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2021;14:e009879.
31 Björklund E, Stenestrand U, Lindbäck J, *et al*. Pre-hospital Thrombolysis delivered by Paramedics is associated with reduced time delay and mortality in ambulance-transported real-life patients with ST-elevation myocardial infarction. *Eur Heart J* 2006;27:1146–52.
32 Mannsverk J, Steigen T, Wang H, *et al*. Trends in clinical outcomes and survival following Prehospital thrombolytic therapy given by ambulance Clinicians for ST-elevation myocardial infarction in rural sub-Arctic Norway. *Eur Heart J Acute Cardiovasc Care* 2019;8:8–14.

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