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Influence of gender on delays and early mortality in ST-segment elevation myocardial infarction: Insight from the first French Metaregistry, 2005–2012 patient-level pooled analysis☆

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ABSTRACT

Background: Women show greater mortality after acute myocardial infarction. We decided to investigate whether gender affects delays and impacts in-hospital mortality in a large population.
Methods and results: We performed a patient-level analysis of 7 French MI registries from different regions from January 2005 to December 2012. All patients with acute STEMI were included within 12 h from symptom onset and a first medical contact with a mobile intensive care unit an emergency department of a hospital with percutaneous coronary intervention facility. Primary study outcomes were STEMI, patient and system, delays. Secondary outcome was in-hospital mortality. 16,733 patients were included with 4021 females (24%). Women were significantly older (mean age 70.6 vs 60.6), with higher diabetes (19.6% vs 15.4%) and hypertension rates (58.7% vs 38.8%). Patient delay was longer in women with adjusted mean difference of 14.4 min ($p < 0.001$); system delay did not differ. In-hospital death occurred 3 times more in women. This disadvantage persisted strongly adjusting for age, therapeutic strategy and delay with a 1.85 (1.32–2.61) adjusted hazard ratio.
Conclusions: This overview of 16,733 real-life consecutive STEMI patients in prospective registries over an extensive period strongly indicates gender-related discrepancies, highlighting clinically relevant delays in seeking medical attention. However, higher in-hospital mortality was not totally explained by clinical characteristics or delays. Dedicated studies of specific mechanisms underlying this female disadvantage are mandatory to reduce this gender gap.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Coronary artery disease is the leading cause of mortality in Western countries [1,2]. Women have been shown to be at greater risk of dying after acute myocardial infarction (MI), particularly in ST-segment elevation MI (STEMI) [3–14], with frequently observed poorer prognosis and higher death rates, especially during in-hospital and short-term follow-up [6,8,13,15–19]. Sex differences in STEMI have been reported regarding baseline characteristics, with greater age and higher prevalence of type-2 diabetes, hypertension and dyslipidemia in females [3,4,7,11,18,20–23]. Procedural characteristics also vary according to gender, with less use of pre-hospital fibrinolysis and of invasive strategies. However, the impact of gender appears to diminish after control for age and comorbidities [7,11]. Nonetheless, registry results highlight differences in time management [21,24,25], mainly regarding call time and catheterization laboratory (cath lab) transfer time, with longer delays for females, but again modified by adjustment. Time to treatment is known to be an essential predictor of fatal outcome in STEMI patients [26–32]. However, the respective roles of each component of time to treatment need to be specified: the patient's delay in seeking medical attention and the health system's delays (door-to-balloon time). These delays have to be analyzed in the contemporary setting of organized networks and widespread use of percutaneous coronary intervention (PCI) for STEMI.

The present study investigated whether gender influenced STEMI delays (patient and system delays and ischemic time), which delay was the most influenced, and whether the effect of gender on early outcome after STEMI, in terms of in-hospital mortality, was mediated by longer delays.

A patient-level pooled analysis was therefore performed, including patients from French registries (the French Metaregistry collection) over a long period of time and from different regions, to investigate the impact of gender, with increased statistical power by including real-world STEMI patients treated by primary PCI (pPCI) and/or by fibrinolysis. It was hypothesized that this data collection would enable precise study of the various components of STEMI delays and of whether, after adjustment, these delays are critically different according to gender and clinically relevant.

1. Methods

1.1. Registries

MI registries were developed to provide updated, exhaustive and validated data on morbidity and mortality from cardiovascular causes, to define patient profiles, and to identify therapeutic strategies in MI. For many years in France, regional registries have been kept up, some as part of care networks of cardiologists and emergency physicians, to monitor practice and improve the care process, including rates and forms of reperfusion [33].

The present study pooled patient-level data to provide large validated data on the acute issue of gender discrepancies. This surrogate of a national database provides, for the first time, a complete overview, allowing comparison with data collected in other countries, and should help to design strategies for improvement and educational campaigns.

All the principal investigators in all existing French registries and surveys, except one, agreed to participate and share patient-level data (**online supplement eTable 1**).

All the registries, despite some methodological differences, used the same care logistics protocols, with similar networking between hospitals and pre-hospital medical services. They all used the same definition of STEMI, following national and international guidelines [34]. Particular attention was paid to homogeneity of data. Data characteristics are summarized in the online supplement. These registries collect data from very varying regions, differing in population density, urban or rural predominance, geographical characteristics, and availability and distribution of interventional cardiology centers. This diversity should allow extrapolation of the present results to other countries.

1.2. Patients

The study population consisted of all patients included in the participant registries from January 2005 to December 2012. STEMI was defined by typical chest pain lasting >20 min and <12 h and ST elevation >0.2 mV in men or 0.15 mV in women in ≥2 precordial leads or >0.1 mV in ≥2 frontal leads or left bundle branch block. Only patients whose first medical contact was an emergency department with PCI facility or a mobile intensive care unit (MICU) were included. The French emergency healthcare system is highly medicalized: in case of chest pain, patients are encouraged to call the emergency medical dispatch center (by phoning 15 or 112); after assessing the probability of acute MI, the emergency physician can dispatch a MICU with a physician on board. Patients presenting out-of-hospital cardiac arrest prior to the first medical contact (FMC) were excluded. To maintain data consistency for the examination of trends, patients directly admitted to a coronary care unit were also excluded.

Whereas registries collect data on a standardized set of clinical, demographic and procedural variables along with in-hospital outcome, the present study focused only on data for demographics, time to call and to treatment, reperfusion strategy, initial antithrombotic drugs (when known) and in-hospital mortality.

1.3. Outcomes

The primary outcome measures of the study were the various STEMI delays [34]: *patient delay*, from symptom onset until call to emergency service (15 or 112) or until presentation at the emergency department (as reported by the patient); *system delay*, from FMC (presentation at the emergency department or arrival of the MICU team) to thrombolysis or pPCI puncture; and *total ischemic time*, from symptom onset to pPCI or thrombolysis, defined as time of puncture, as reported in all the registries. The influence of gender on these delays was assessed, initially without adjustment, and then stratified by age and risk factors.

The secondary outcome was in-hospital mortality, which included death from any cause occurring during the index hospitalization for STEMI, with assessment of the influence of gender, age risk factors, therapeutic strategy and delays.

Using this unique innovative French database, regional differences were represented. Changes were assessed over the whole from 2005 to 2012.

1.4. Data management

For each patient, standardized data collection was performed using the specific registry case report form (CRF). Demographic, clinical, delay and treatment data, drugs and reperfusion strategies and in-hospital mortality were collected prospectively by emergency physicians and cardiologists and recorded on each registry's CRF. CRFs were anonymous, in accordance with the French data protection commission (*Commission Nationale de l'Informatique et des Libertés*) guidelines; data collection complied with the Declaration of Helsinki and was approved by local institutional review boards. For each registry, a research assistant checked completeness of data and follow-up. Data quality was regularly controlled within each registry, with regular audits confirming reproducibility.

1.5. Study design and oversight

The study was designed by the first and last author and approved by the scientific committee. The scientific committee, composed of principal or representative investigators of each participant registry, reviewed and approved the proposal.

The authors vouch for the accuracy and completeness of the data and the analysis.

1.6. Statistical analysis

Patient characteristics at baseline were described for the study population and for each group (male, female). Continuous variables were reported as mean plus or minus standard deviation and categorical variables as absolute and relative frequencies (percentages). Categorical variables were compared between men and women using chi-square test, or Fisher's exact test as appropriate; continuous variables were compared using Student's *t*-test for normal distributions or on non-parametric tests for non-normal distributions. Normal distribution was assessed for each variable on Shapiro-Wilk test.

Mean delays (i.e., patient delay, ischemic time and system delay) were compared between men and women using Student's *t*-test and mean differences were reported with 95% confidence intervals. The estimated marginal means of the delays, plus or minus standard error, adjusted on age, region, year of enrolment and emergency call (yes/no), were compared using a generalized linear model and mean differences were reported with 95% confidence intervals. Means were considered statistically different when the p-value was <0.05.

To determine risk factors for in-hospital mortality, univariable analysis was performed for each possible factor, using a logistic regression model. Variables with prevalence >3% and p-value <0.15 were included in a multivariable logistic regression model, after checking correlations between variables of interest; if variables were significantly correlated, the variable to be included in the multivariate model was selected according to clinical relevance or on the Akaike information criterion for multivariable models, performed on the correlating variables. Interactions were also tested; in case of significant interaction between variables, an interaction term was included in the multivariate model. All tests were 2 tailed. A variable was considered to be an independent risk factor for mortality when the p-value was <0.05 in the multivariate model. Statistical analyses were performed using SPSS software (version 20.0; SPSS Inc., Chicago, Illinois).

2. Results

Between 2005 and 2012, 18,618 consecutive STEMI patients were included prospectively in the 7 participating French registries (**online supplement eTable 1**). Due to the strict exclusion criteria, the population was homogenous and confounding factors linked to modality of inclusion (MICU or interventional cardiology center) were limited.

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