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Deleterious synergistic effects of acute heart failure and diabetes mellitus in patients with acute coronary syndrome: Data from the FAST-MI Registries

Abbreviated title: Acute heart failure and diabetes mellitus in patients with ACS

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Summary

Background. – Diabetes mellitus (DM) predisposes patients to acute myocardial infarction (AMI) and acute heart failure (AHF).

Aims. – To assess correlates of AHF occurring at the early stage of AMI and synergism between early AHF and DM on 5-year mortality.

Methods. – FAST-MI 2005 and 2010 included 7839 consecutive patients admitted for AMI.

Results. – Overall, 2151 patients (27.4%) had a history of diabetes mellitus (DM), of whom 629 (29.2%) were on insulin. Patients with versus without DM were older (mean age: 70.0 vs 64.7 years; $P < 0.001$), with more comorbidities and more severe coronary artery disease. Early AHF (pulmonary oedema or cardiogenic shock) was the most frequent in-hospital complication (12.5%) and was twice as frequent in patients with versus without DM (20.2% vs 9.6%; adjusted odds ratio 1.66, 95% confidence interval [CI] 1.43–1.94; $P < 0.001$). Among in-hospital survivors, patients with DM without AHF and those with AHF without DM had 50% increases in 5-year mortality (adjusted hazard ratio [aHR] 1.50, 95% CI 1.32–1.69 and aHR 1.46, 95% CI 1.23–1.74; both $P < 0.001$) versus patients without DM or AHF; with the risk among those with DM and AHF being doubled (aHR 1.97, 95% CI 1.66–2.34; $P < 0.0001$).

Conclusion. – Early AHF is the most frequent complication of AMI and is twice as common in patients with versus without DM. After adjustment, early AHF and DM are associated with reduced 5-year survival with synergistic effects in patients with both conditions.

Clinical Trial Registration. <https://clinicaltrials.gov> (NCT00673036 and NCT01237418).

Résumé

Contexte. – Le diabète (DM) est un facteur de risque majeur d'infarctus aigu du myocarde (IDM) et d'insuffisance cardiaque aiguë (ICA).

Objectifs. – Cette étude a évalué les facteurs pronostiques à la phase aiguë de l'IDM et la synergie entre l'ICA et le DM sur la mortalité à 5 ans.

Méthodes. – Les registres français sur l'IDM (FAST-MI) 2005 et 2010 ont inclus 7839 patients consécutifs admis pour un IDM.

Résultats. – Globalement, 2151 patients (27.4 %) présentaient un DM, parmi eux, 629 (29.2 %) étaient traités par insuline à l'admission. Les patients avec un DM étaient plus âgés (70.0 vs 64.7 ans;

$P < 0.001$), avec plus de comorbidités et une maladie coronarienne plus sévère. L'ICA (œdème pulmonaire ou choc cardiogénique) était la complication hospitalière la plus fréquente (12,5 %) et était deux fois plus fréquente chez les patients diabétiques (20,2 % vs 9,6 % ; odds ratio ajusté 1,66, intervalle de confiance [IC] à 95% 1,43–1,94 ; $P < 0,001$). Chez les patients après sortie d'hospitalisation, par rapport aux patients sans DM ni ICA, ceux avec DM sans ICA et ceux avec ICA sans DM avaient une augmentation de 50 % de la mortalité à 5 ans (risque relatif ajusté 1,50, IC à 95 % 1,32–1,69 ; $P < 0,001$ et risque relatif ajusté de 1,46, IC à 95 % 1,23–1,74 ; $P < 0,001$) tandis que le risque de mortalité à 5 ans était doublé chez les patients atteints de DM et d'ICA (risque relatif ajusté de 1,97, IC à 95 % 1,66–2,34 ; $P < 0,0001$).

Conclusion . – L'insuffisance cardiaque aiguë est la complication la plus fréquente de l'infarctus aigu du myocarde durant l'hospitalisation et est deux fois plus fréquente chez les patients diabétiques. Après ajustement, l'insuffisance cardiaque aiguë et le diabète sont associés à une survie réduite à 5 ans avec un effet synergique chez les patients atteints des deux affections.

KEYWORDS

Acute heart failure;

Acute myocardial infarction;

Diabetes mellitus;

Long-term outcomes

MOTS-CLÉS

Insuffisance cardiaque aiguë ;

Infarctus aigu du myocarde ;

Diabète ;

Résultats à long terme

Abbreviations: AHF, acute heart failure; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CI, confidence interval; DM, diabetes mellitus; DM_i, diabetes mellitus with insulin; DM_{ni}, diabetes mellitus without insulin; FAST-MI, French registries of Acute ST-elevation and non-ST-elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events; HF, heart failure;

HR, hazard ratio; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction, OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

Background

The prevalence of type 2 diabetes mellitus (DM) has increased in the general population and may reach 350 million people by 2030 [1]. Between 1980 and 2014, the number of people with DM quadrupled and the age-standardized prevalence among adults increased significantly during that time [2]. Cardiovascular diseases are the leading cause of death in the world and with improved control over other cardiovascular risk factors, the burden of cardiovascular disease attributable to DM is increasing [3]. Cardiovascular mortality is 2–4-fold higher among patients with diagnosed DM than among those without diagnosed DM [4,5].

Among patients with acute myocardial infarction (AMI), cardiovascular mortality has decreased from 1995 to 2015 in parallel with greater use of myocardial revascularization and recommended medications in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) [6]. Patients with DM, however, remain at higher risk for subsequent events, including acute heart failure (AHF) and death, independently of other comorbidities [7,8]. Several clinical and pathophysiological mechanisms may play roles in the unfavourable prognosis of DM, including insulin resistance, hyperglycaemia, endothelial dysfunction, inflammation and greater platelet activation, but also increased delays in presentation and diagnosis, less reperfusion therapy and a greater burden of atherosclerotic disease [9]. Randomized studies have confirmed the worse prognosis of AMI in patients with DM [10,11].

In addition to AMI and other atherosclerosis-related events, AHF is a major contributor to cardiovascular death in patients with type 2 DM [12]. In the Framingham study [13], risk of AHF was 2.4-fold in men and 5.0-fold in women for those with versus without DM. Multiple factors, including age, ischaemic heart disease and peripheral artery disease, as well as DM-specific risk factors, such as poor glycaemic control and insulin resistance, have been associated with heart failure (HF) in patients with DM [14-17]. The pathogenesis of AHF is complex and multifactorial, associating metabolic perturbations, functional alterations, structural changes and neurohormonal dysregulation. Special consideration should be also taken in glycaemic management as some antidiabetic drugs increase the risk of AHF [18]. Moreover, recent studies have shown that inhibitors of sodium-glucose cotransporter 2 reduced hospitalization for AHF in patients with type 2 DM [19-21].

Therefore, we decided to explore the synergistic effect of early AHF and DM in patients admitted for AMI. Using the French registries of Acute ST-elevation and non-ST-elevation Myocardial

Infarction (FAST-MI) 2005 and 2010, we assessed correlates of the occurrence of AHF at the acute stage of AMI, and the synergism between early AHF and DM on 5-year mortality in patients admitted for NSTEMI or STEMI.

Methods

Study design

All patients from the two nationwide French registries – FAST-MI 2005 and 2010 – were included. The methods of the FAST-MI registries have previously been described in detail [22,23]. Briefly, the two registries included consecutive adult patients with NSTEMI or STEMI over 1-month periods in 2005 and 2010. In 2005, inclusion was extended by 1 additional month for patients with a history of diabetes; in 2010, voluntary centres could prolong inclusion of any patients for up to 1 additional month. Participation in the registries was offered to all French institutions, university teaching hospitals, general and regional hospitals and private clinics with intensive care units with the capacity to receive acute coronary syndrome emergencies. Their primary objectives were to: provide an extensive description of the population of patients admitted for AMI; collect extensive data on practices for myocardial infarction (MI) management; and evaluate short- and long-term outcomes. Patients were included if they: (1) were over 18 years of age; (2) were admitted within 48 hours of symptom onset in a cardiology department for an AMI, defined as an elevation of troponins or creatinine kinase myocardial band and at least one of the following: symptoms compatible with myocardial ischaemia, development of new abnormal Q waves or ST-T changes compatible with myocardial ischaemia and (3) agreed to participate. Patients with unstable angina were not included. Those with iatrogenic AMI were excluded, as were those initially suspected of AMI in whom this diagnosis was subsequently disproved. All data were collected prospectively and were recorded on computerized case record forms by dedicated research technicians in each of the centres. In 2005 (clinicaltrials.gov identifier: NCT00673036), 3670 patients were recruited in 223 centres, and in 2010 (clinicaltrials.gov identifier: NCT01237418), 4169 patients were recruited in 213 centres.

Baseline characteristics and follow-up

Data on baseline characteristics – including demographics, risk factors and medical history – were prospectively collected as previously described [22,23]. Patients with DM were defined as those with a

known history of DM (with or without medications). Incident DM was defined as patients without known DM on admission but treated with antidiabetic drug(s) at discharge. All other patients were considered as not having DM. For both cohorts, centralized follow-up was organized by the French Society of Cardiology and performed by dedicated research technicians of 'Unite de recherche Clinique de l'Est Parisien'.

In-hospital outcomes (death, recurrent MI, stent thrombosis, AHF, bleeding or transfusion) and 1- and 5-year mortality were collected. Early AHF was defined as Killip class III (pulmonary oedema) or IV (cardiogenic shock) during index hospitalization using the classification of Killip and Kimball [24]. Recurrent MI was defined as recurrence of clinical symptoms or occurrence of electrocardiogram changes accompanied by a recurrent increase in cardiac markers. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium definition. Bleeding was classified as major or minor according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Follow-up data were collected through contact with the attending physicians and the patients or their family. If missing, vital status was assessed from the civil registries of the patient's birthplaces. Vital status at 5 years could be assessed in 97% of FAST-MI 2005 and > 95% of FAST-MI 2010 patients.

The registry was conducted in compliance with Good Clinical Practice guidelines, French law and the French data protection law. The protocol was reviewed and approved by the Committee for the Protection of Human Subjects of Saint-Louis University Hospital, and the data file of FAST-MI was declared to the Commission Nationale de l'Informatique et des Libertés. All patients gave informed consent for their participation in the studies.

Statistical analysis

Continuous variables were analysed for a normal distribution with the D'Agostino-Pearson test. Continuous variables are presented as means and standard deviations (SDs) if normally distributed and compared with Student's unpaired *t* test, or as medians and interquartile ranges (IQRs) if not, and compared with Mann-Whitney rank-sum test. Categorical variables are presented as numbers and percentages and were compared by means of the χ^2 test or Fisher's exact test. Binary logistic regression analysis was used to determine whether DM was an independent correlate of AHF with adjustment on clinically relevant covariables: risk factors, previous medical history, type of MI, year of survey and medications used before the index MI. Odds ratios (ORs) and adjusted ORs are given with

their 95% confidence intervals (CIs). For event-free survival analyses, only patients with follow-up data available were included in the analyses. Long-term survival curves were estimated using the Kaplan–Meier method and comparisons were made using log-rank tests. Independent predictors of events during follow-up were determined using a stepwise multivariable Cox regression analysis and adjusted hazard ratios (HRs) were calculated with 95% CIs. For adjustment, variables that were predictive of events in univariate analysis ($P < 0.20$) were entered in the multivariable model. Statistical analyses were performed using IBM SPSS 25.0 (IBM SPSS Inc.). For all analyses, a two-sided P -value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 7839 patients included in the registries, 2151 (27.4%) presented with DM. Of these, 629 (29.2%) were treated with insulin (DM_i), with the remainder having no insulin treatment (DM_{ni}). The flowchart of the study is presented in [Fig. 1](#). Baseline characteristics of the different groups are presented in [Table 1](#). Patients with versus without DM were older and more likely to have risk factors (hypertension, hyperlipidaemia or obesity) but less likely to be smokers or have a family history of coronary artery disease. Comorbidities (e.g. previous MI and history of HF) were also more frequent in patients with DM, as was previous treatment with various cardiovascular medications. STEMI was less frequent in patients with DM. Fewer patients with versus without DM underwent coronary angiography (81.9% vs 93.1%; $P < 0.0001$). Percutaneous coronary intervention (PCI) was performed in 61.4% of patients with DM compared to 75.5% of those without ($P < 0.0001$), while coronary artery bypass graft (CABG) during the initial hospital stay was performed more frequently patients with versus without DM (4.5% vs 2.9%; $P < 0.001$).

Among patients with STEMI, median (IQR) time to admission was significantly longer in patients with versus without DM: 215 (120–522) versus 180 (110–385) minutes; $P < 0.001$; the rate of reperfusion therapy (thrombolysis or primary PCI) was also significantly lower (63.3% vs 76.4%; $P < 0.001$). Among patients with NSTEMI, the rate of coronary angiography was lower in patients with versus without DM (81.2% vs 87.3%; $P < 0.001$) and PCI was performed less often (53.0% vs 61.0%; $P < 0.001$).

AHF, DM, and in-hospital outcomes

During hospitalization, AHF occurred in 9.6% of patients without DM and 20.2% of patients with DM (crude OR 2.40, 95% CI 2.09–2.75; $P < 0.0001$; adjusted OR 1.66, 95% CI: 1.43–1.94; $P < 0.001$) (Fig. 2; Table A.1). AHF was more frequently observed in patients with DM on insulin therapy (29.1%) compared to those not receiving insulin (16.6%) (Fig. 2; Table A.1). In patients with DM, insulin therapy use before AMI was an independent correlate of AHF occurrence (OR 1.61, 95% CI 1.26–2.05; $P < 0.001$); other independent correlates are listed in Table A.2. In the FAST-MI 2010 registry, diuretics were used within 48 hours of admission in 43.9% of patients with DM compared to 22.6% of patients without DM ($P < 0.001$). Left ventricular ejection fraction was $49 \pm 12\%$ versus $53 \pm 11\%$ in patients with versus without DM, respectively ($P < 0.001$). These data were not available in the FAST-MI 2005 registry. Although various complications were more frequent in patients with DM, stroke (0.7% vs 0.6%; $P = 0.62$) and bleeding complications were not significantly different between the two groups (Fig. 2; Table A.1). In-hospital mortality was higher in patients with DM (6.1% vs 3.5%; $P < 0.0001$).

All types of in-hospital complications (ischaemic, haemorrhagic, rhythm disturbances) were more frequent in patients who had AHF, irrespective of their diabetic status. In patients without heart failure, in-hospital mortality was higher in patients with DM (2.4% vs 1.4%; $P = 0.008$), whereas mortality in patients with AHF was similar for patients with or without DM (20.9% vs 23.1%, respectively; $P = 0.419$; Table 2)

The significant difference in early AHF and in-hospital death between patients with and without DM was found in patients with STEMI or NSTEMI (AHF: 21.3% vs 11.9% in NSTEMI, 18.8% vs 8.0% in STEMI; in-hospital death: 5.2% vs 3.0% in NSTEMI; 7.3% vs 3.9% in STEMI).

Long-term mortality according to DM status and occurrence of AHF

Crude all-cause mortality was significantly higher in patients with versus without DM at 1 year (17.8% vs 8.7%; $P < 0.0001$) and 5 years (38.2% vs 19.3%; $P < 0.0001$) (Table A.1). The lowest mortality rates at 1 and 5 years were observed in patients without DM or AHF (5.7% and 14.7%, respectively) and highest in patients with DM and AHF (30.4% and 69.0%, respectively) as illustrated in Table 2. After adjustment for confounders, compared with patients with neither DM nor AHF, those with DM without AHF and those with AHF without DM had increases in 5-year mortality of similar magnitude

(adjusted HR 1.50, 95% CI 1.32–1.69 and adjusted HR 1.46, 95% CI 1.23–1.74, respectively; both $P < 0.001$), while the highest mortality risk was observed in patients with both DM and AHF (adjusted HR 1.97, 95% CI 1.66–2.34; $P < 0.001$) as illustrated in Fig. 3. A significant interaction existed between early AHF and DM for 5-year survival ($P_{\text{interaction}} < 0.001$).

Incident versus prevalent DM

Among patients surviving the index hospital stay, the population of patients with incident DM was small ($n = 183$) compared to those with prevalent DM ($n = 2023$), but these patients had different characteristics. Those with incident versus prevalent DM were younger (63.6 ± 13.1 vs 69.7 ± 11.7 years; $P < 0.0001$), more frequently male (80.9% vs 67.7%, $P < 0.001$) and had less comorbidities (Global Registry of Acute Coronary Events [GRACE] score: 140 ± 38 vs 150 ± 37 ; $P = 0.001$; creatinine: 10.0 ± 3.5 vs 12.6 ± 9.2 mg/L; $P < 0.001$). Interestingly, body mass index (28.6 ± 4.9 vs 28.7 ± 5.0 kg/m²; $P = 0.747$) and glycaemia (194 ± 83 vs 203 ± 94 mg/dL; $P = 0.235$) were similar in both groups, but haemoglobin A1c was higher in patients with incident DM ($7.8 \pm 1.8\%$ vs $7.5 \pm 1.5\%$; $P = 0.017$). During hospitalization, AHF occurred in 13.1% of patients with known DM ($P = 0.172$). Outcomes by DM status (incident versus prevalent) and occurrence of AHF are presented in [Table A.3](#).

Cox logistic regression was performed among hospital survivors to determine whether AHF, incident DM and prevalent DM were independent predictors of long-term mortality. After adjustment for confounders, compared with an absence of DM and AHF, incident DM without or with AHF was not associated with increased 5-year mortality (adjusted HR 1.05, 95% CI 0.67–1.64; $P = 0.83$ and adjusted HR 0.87, 95% CI 0.45–1.70; $P = 0.68$, respectively). AHF and prevalent DM were associated with increases in 5-year mortality of similar magnitude (adjusted HR 1.29, 95% CI 1.06–1.57; $P = 0.01$ and adjusted HR 1.51, 95% CI 1.34–1.72; $P < 0.001$, respectively), while the highest mortality rate was observed in patients with both prevalent DM and AHF (adjusted HR 1.69, 95% CI 1.40–2.04; $P < 0.001$).

Discussion

In these large registries of patients admitted for AMI, AHF was the most frequent complication during initial hospitalization, and was twice as common in patients with versus without DM. Both DM without

AHF, and occurrence of AHF without a history of DM were associated with a 50% increase in 5-year mortality, while the combination of DM and AHF was associated with twice the risk of 5-year death, compared with that of patients with neither DM nor AHF.

Baseline characteristics of patients with DM

History of DM was more frequent in patients with NSTEMI than in those with STEMI, in line with previous reports [25-27]. Also as previously observed, patients with versus without DM were older and had more risk factors (except for current smoking) and more comorbidities, including previous history of HF [10,11,28]. Comorbidities were particularly prevalent in patients with DM on insulin therapy before the AMI. During hospitalization, patients with DM less often underwent angiography and PCI compared with those without DM, as previously reported [10,11,29].

Type of in-hospital complications according to DM status

At the acute stage of AMI, AHF is the most frequent complication, being more common than death or ischaemic events. Here, early AHF (pulmonary oedema or cardiogenic shock) occurred in one in five DM patients versus one in 10 patients without DM. Previous research on HF complicating MI has been conducted in patients with STEMI [30,31], in whom Killip class ≥ 2 has been reported in 19.1–32.4%. In the GRACE registry, Killip class 2 or 3 was present in 13% of patients admitted for MI [32]. Likewise, Bahit et al. demonstrated that 10.6% of patients with NSTEMI had Killip class ≥ 2 at admission and an additional 2.9% during hospitalization [33], and DM was one of the predictors of HF at admission or during hospitalization (OR 1.6). None of these studies specifically focused on patients with DM. In our study, Killip class ≥ 2 was present in 20.0% of the whole population, with 25.8% in patients with DM_{ni} and 41.2% in patients with DM_i. In-hospital death and reinfarction were also more frequent in patients with DM but the rate of these events was much lower than that of the AHF.

Impact of early AHF on long-term mortality

Early AHF was associated with increased 5-year mortality in patients with or without DM. As described in previous studies, development of AHF during hospitalization was associated with a worse prognosis [31,32]. Interestingly, however, we found that 5-year mortality was similarly increased in patients with AHF and without DM, and in those with DM and no AHF. After taking confounders into account,

patients with DM who developed AHF had twice the risk of being dead at 5 years compared with patients with neither DM nor AHF. Of note, we observed that recommended therapy, including myocardial revascularization, was less frequently used in patients with DM. Several studies have demonstrated the impact of revascularization in patients with STEMI and NSTEMI, as supported by American College of Cardiology/American Heart Association or European Society of Cardiology guidelines [34-36]. Likewise, recommended medications should be prescribed in patients with DM as in those without [37,38].

New antidiabetic drugs that have been shown to improve cardiovascular outcomes in patients with DM were not available at the time of the surveys. It is likely that substantial progress could be achieved with the use of such medications, particularly in the case of AHF complicating the AMI. Glucagon-like peptide-1 receptor agonists are effective glucose-lowering drugs and can reduce major adverse cardiovascular events and cardiovascular mortality [39]. Whereas clinical benefit could be present in patients with AMI, developing AHF remains conjectural and prospective studies are necessary. Selective inhibitors of sodium-glucose cotransporter 2 that promote glucosuria in patients with type 2 DM have not been shown to result in a lower rate of cardiovascular death or hospitalization for HF [20,40,41]. Recently, dapagliflozin demonstrated a reduction in the risk of HF recurrence or death from cardiovascular causes among patients with HF and reduced ejection fraction, regardless of the presence or absence of DM [42]. Recent guidelines have upgraded the positioning of these new drugs in the armamentarium available for patients with DM [43]. Whether similar or greater benefits could be found in patients with AMI who develop AHF will have to be assessed in future studies.

Incident versus prevalent DM

Incident DM in the present study was uncommon and underestimated compared to previous studies, which have reported a rate of about 10% of new cases [44,45]. Moreover, incident DM was not a predictive factor of 5-year mortality in hospital survivors, unlike prevalent DM or AHF. Previous studies have shown that new hyperglycaemia increases the risk of mortality [46], but the impact of incident DM is still unclear [47]. A prospective study with a larger number of patients would be interesting to assess the risk of mortality in patients with incident versus prevalent DM.

Study limitations

This study has several limitations. First, the FAST-MI registries included consecutive patients with NSTEMI or STEMI admitted to intensive cardiac care units. The most severe patients, particularly those with an initial cardiac arrest, may have been admitted to general intensive care units rather than to specialized cardiac care units, and may therefore not have been included. This could bias the sample towards a somewhat lower risk group. We based our definition of DM on the presence of a history of DM. However, as has been previously shown, AMI may reveal previously undiagnosed DM [48]. Secondly, AHF was assessed by clinical examination using the Killip and Kimball classification. No biomarkers (e.g. B-type natriuretic peptide or N-terminal pro B-type natriuretic peptide) or diastolic parameters by echocardiography were used routinely to confirm the diagnosis of AHF. To be certain of the presence of in-hospital AHF, we deliberately defined early AHF as the presence of Killip class 3 or 4 during hospitalization, as Killip class 2 is more prone to subjective interpretation of clinical signs. The frequency of early AHF in the current study is, therefore, possibly underestimated. Finally, early AHF was found to be an independent factor of mortality in patients with and without DM using multivariable analysis. However, no causality can be demonstrated and unmeasured confounding variables may exist, even though the FAST-MI registries collected a considerable number of items and therefore improved the quality of adjustments.

Conclusions

AHF is the most frequent complication after NSTEMI or STEMI and is much more common in patients with DM. It is associated with reduced 5-year survival in patients with and without DM. The association of AHF and DM identifies a particularly high-risk subgroup in all types of AMI. At the acute stage of AMI, new management strategies are needed to avoid occurrence of AHF, particularly in patients with DM, and to improve survival in these patients at very high risk.

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Contributorship statement

J.-G. D.: Study planning, study analysis, drafting the manuscript and responsible for the overall content as guarantor.

G. A.: collecting data, study analysis, drafting the manuscript.

F. A. and J.-N. L.: contribution to data acquisition, analysis.

G. M.: contribution to analysis and critical revision.

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E. P.: study conception and design, analysis, critical revision.

T. S.: study supervision and responsible for the overall content as guarantor.

N. D.: study conception and design, study analysis, critical revision and responsible for the overall content as guarantor.

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Figure legends

Figure 1. Flowchart of the study according to status of diabetes mellitus (DM).

Figure 2. In-hospital outcomes (stroke, non-fatal MI, AHF, death and TIMI major or minor bleeding) in patients without DM, in all patients with DM and in patients with DM treated without and with insulin .

AHF: acute heart failure. DM: diabetes mellitus; DM_i: diabetes mellitus with insulin; DM_{ni}: diabetes mellitus without insulin; MI: myocardial infarction.

$P < 0.05$ for DM versus no DM.* $P < 0.05$ for DM_{ni} versus no DM.

† $P < 0.05$ for DM_i versus DM_{ni}.

DM indicates diabetes mellitus

MI indicates myocardial infarction

TIMI indicates Thrombolysis in myocardial infarction

Figure 3. Five-year survival according to presence or absence of DM and/or early AHF.AHF: acute heart failure; CI: confidence interval; DM, diabetes mellitus; HR, hazard ratio.

Graphical abstract. Characteristics of the study population and 5-year survival according to the presence or absence of DM and/or early AHF.

Table 1 Baseline patient characteristics according to presence or absence of DM and according to DM treatment.

	Overall (<i>n</i> = 7839)	No DM (<i>n</i> = 5688)	DM (<i>n</i> = 2151)	DM _{ni} (<i>n</i> = 1522)	DM _i (<i>n</i> = 629)	<i>P</i> (DM vs no DM)	<i>P</i> (DM _{ni} vs DM _i)
Age (years)	66.1 ± 14.2	64.7 ± 14.7	70.0 ± 11.6	69.2 ± 11.7	72.1 ± 11.3	< 0.001	< 0.001
Age > 75 years	2517 (32.1)	1668 (29.3)	849 (39.5)	547 (35.9)	302 (48.0)	< 0.001	<0.001
Male	5545 (70.7)	4102 (72.1)	1443 (67.1)	1098 (72.1)	345 (54.8)	<0.001	< 0.001
Risk factors							
BMI (kg/m ²)	27.0 ± 4.7	26.4 ± 4.4	28.6 ± 5.1	28.7 ± 5.1	28.5 ± 5.1	< 0.001	0.453
	<i>n</i> =7174	<i>n</i> =5248	<i>n</i> =1926	<i>n</i> =1367	<i>n</i> =559		
BMI ≥ 25 and < 30 kg/m ²	3033 (42.3)	2207 (42.1)	826 (38.4)	601 (44.0)	225 (35.8)	<0.001	0.287
BMI ≥ 30 kg/m ²	1590 (22.2)	932 (17.8)	658 (30.6)	462 (33.8)	196 (35.1)		
Hypertension	4413 (56.3)	2772 (48.7)	1641 (76.3)	1140 (74.9)	501 (79.7)	< 0.001	0.018
Dyslipidaemia	3580 (45.7)	2338 (41.1)	1242 (57.7)	855 (56.2)	387 (61.5)	< 0.001	0.022
Family history	1908 (24.3)	1505 (26.5)	403 (18.7)	303 (19.9)	100 (15.9)	< 0.001	0.030
Current smoker	2527 (32.2)	2104 (37.0)	423 (19.7)	339 (22.3)	84 (13.4)	< 0.001	< 0.001
Medical history							
MI	1308 (16.7)	750 (13.2)	558 (25.9)	326 (21.4)	232 (36.9)	< 0.001	< 0.001
PCI	1140 (14.5)	648 (11.4)	492 (22.9)	291 (19.1)	201 (32.0)	< 0.001	< 0.001
CABG	459 (5.9)	270 (4.7)	189 (8.8)	111 (7.3)	78 (12.4)	< 0.001	< 0.001

	Overall (n = 7839)	No DM (n = 5688)	DM (n = 2151)	DM _{ni} (n = 1522)	DM _i (n = 629)	P (DM vs no DM)	P (DM _{ni} vs DM _i)
Heart failure	388 (4.9)	202 (3.6)	186 (8.6)	88 (5.8)	98 (15.6)	< 0.001	< 0.001
PAD	692 (8.8)	378 (6.7)	314 (14.6)	175 (11.5)	139 (22.1)	< 0.001	< 0.001
Atrial fibrillation ^a	239 (5.7)	166 (5.0)	73 (8.7)	47 (7.8)	26 (11.0)	0.005	0.144
	n=4169	n=3334	n=835	n=599	n=236		
Chronic renal failure	383 (4.9)	172 (3.0)	211 (9.8)	88 (5.8)	123 (19.6)	< 0.001	< 0.001
COPD	450 (5.7)	302 (5.3)	148 (6.9)	93 (6.1)	55 (8.7)	0.008	0.028
Previous treatment							
Aspirin	1844 (23.5)	1099 (19.3)	745 (34.6)	446 (29.3)	299 (47.5)	< 0.001	<0.001
Clopidogrel	994 (12.7)	531 (9.3)	463 (21.5)	253 (16.6)	210 (33.4)	< 0.001	<0.001
Prasugrel ^a	13 (0.3)	8 (0.1)	5 (0.2)	4 (0.3)	1 (0.2)	0.373	0.649
VKA	388 (4.9)	245 (4.3)	143 (6.7)	93 (6.1)	50 (7.9)	<0.001	0.125
Statins	2182 (27.8)	1300 (22.9)	882 (41.0)	565 (37.1)	317 (50.4)	< 0.001	<0.001
Ezetimibe	142 ()	88 (1.5)	54 (2.5)	29 (1.9)	25 (4.0)	0.004	0.005
ACEI/ARBs	2658 (33.9)	1526 (26.8)	1132 (52.6)	737 (48.4)	395 (62.8)	< 0.001	<0.001
Beta-blockers	1908 (24.3)	1159 (20.4)	749 (34.8)	477 (31.3)	272 (43.2)	<0.001	<0.001
Diuretics	1927 (24.6)	1095 (19.3)	832 (38.7)	508 (33.4)	324 (51.5)	< 0.001	< 0.001
Calcium blockers	1434 (18.3)	814 (14.3)	620 (28.8)	401 (26.3)	219 (34.8)	< 0.001	< 0.001

	Overall (n = 7839)	No DM (n = 5688)	DM (n = 2151)	DM _{ni} (n = 1522)	DM _i (n = 629)	P (DM vs no DM)	P (DM _{ni} vs DM _i)
Nitrates	577 (7.4)	335 (5.9)	242 (11.3)	137 (9.0)	105 (16.7)	< 0.001	< 0.001
Sulfonylureas	281 (3.6)	0 (0.0)	703 (32.7)	625 (41.1)	78 (12.4)	< 0.001	< 0.001
Metformin	864 (11.0)	0 (0.0)	795 (37.0)	673 (44.2)	122 (19.4)	< 0.001	< 0.001
Insulin	629 (8.0)	0 (0.0)	629 (29.2)	0 (0.0)	629 (100.0)	<0.001	< 0.001
MI presentation							
STEMI	4250 (54.2)	3320 (58.4)	930 (43.2)	714 (46.9)	216 (34.3)	< 0.001	< 0.001
NSTEMI	3589 (45.8)	2368 (41.6)	1221 (56.8)	808 (53.1)	413 (65.7)	< 0.001	< 0.001
Parameters on admission							
SBP (mmHg)	142 ± 28 n=7760	141 ± 28 n=5633	146 ± 30 n=2127	146 ± 29 n=1503	146 ± 31 n=624	< 0.001	0.589
Heart rate (bpm)	80 ± 20 n=7763	78 ± 20 n=5636	84 ± 22 n=2127	83 ± 22 n=1503	86 ± 22 n=624	< 0.001	0.009
GRACE score	144 ± 37n n=7479	141 ± 36 n=5439	153 ± 36 n=2040	150 ± 36 n=1437	163 ± 37 n=603	< 0.001	< 0.001
Cardiac arrest	110 (1.4)	88 (1.5)	22 (1.0)	19 (1.2)	3 (0.5)	0.38	0.14
Killip class ≥ 2	1542 (20.0)	901 (16.1)	641 (29.8)	385 (25.8)	256 (41.2)	< 0.001	< 0.001
LVEF (%)	52 ± 12	52 ± 12	49 ± 13	50 ± 13	48 ± 14	< 0.001	0.002

	Overall (n = 7839)	No DM (n = 5688)	DM (n = 2151)	DM _{ni} (n = 1522)	DM _i (n = 629)	P (DM vs no DM)	P (DM _{ni} vs DM _i)
	n=6350	n=4668	n=1682	n=1207	n=475		
Coronary angiography	7043 (89.8)	5211 (91.6)	1832 (85.2)	1358 (89.2)	474 (75.4)	< 0.001	<0.001
Multivessel disease	3729 (53.3)	2562 (49.5)	1167 (64.1)	830 (61.5)	337 (71.5)	< 0.001	<0.001
	N=7000	N=5180	N=1820	N=1349	N=471		
3-vessel disease	1223 (16.3)	808 (14.7)	415 (19.3)	318 (23.6)	120 (25.5)	< 0.001	0.405
				N=1349	N=471		
PCI	5595 (71.4)	4223 (74.2)	1372 (63.8)	1042 (68.5)	330 (52.5)	< 0.001	<0.001
CABG	271 (3.5)	171 (3.0)	100 (4.6)	82 (5.4)	18 (2.9)	< 0.001	0.011
Biological data							
Haemoglobin (g/dL)	13.9 ± 1.9	14.1 ± 1.8	13.4 ± 1.9	13.7 ± 1.9	12.8 ± 2.0	< 0.001	<0.001
	N=7617	N=5543	N=2074	N=1461	N=613		
Creatinine (mg/L)	11.2 ± 7.4	10.6 ± 6.5	11.8 ± 7.9	11.8 ± 8.0	15.2 ± 11.5	< 0.001	<0.001
	N=7655	N=5565	N=2090	N=1472	N=618		
Creatinine clearance (mL/min/1.73m ²)	73 ± 24	76 ± 23	64 ± 25	68 ± 24	55 ± 26	< 0.001	<0.001
	N=7655	N=5565	N=2090	N=1472	N=618		
Glycaemia (mmol/L)	8.4 ± 4.2	7.3 ± 3.1	11.2 ± 5.2	10.9 ± 5.1	11.9 ± 5.6	< 0.001	<0.001
	N=7046	N=5078	N=1968	N=1378	N=590		

	Overall (n = 7839)	No DM (n = 5688)	DM (n = 2151)	DM _{ni} (n = 1522)	DM _i (n = 629)	P (DM vs no DM)	P (DM _{ni} vs DM _i)
A1c level (%) (n = 1698)	6.6 ± 1.4 N=2902	5.9 ± 0.9 N=1759	7.5 ± 1.5 N=1143	7.3 ± 1.5 N=831	8.1 ± 1.5 N=312	< 0.001	< 0.001
LDL-C (mg/dL)	119 ± 43 N=5415	124 ± 43 N=4060	104 ± 40 N=1355	106 ± 39 N=979	98 ± 43 N=376	< 0.001	0.002
HDL-C (mg/dL)	47 ± 15 N=5434	47 ± 15 N=4042	45 ± 15 N=1392	45 ± 15 N=1009	45 ± 17 N=383	< 0.001	0.841
Triglycerides (mg/dL)	146 ± 105 N=5779	141 ± 96 N=4271	160 ± 126 N=1508	163 ± 130 N=1080	152 ± 117 N=428	< 0.001	0.135
CRP (mg/L)	22 ± 47 N=5567	19 ± 43 N=4057	30 ± 52 N=1510	25 ± 46 N=1057	41 ± 66 N=453	< 0.001	< 0.001

Data are expressed as mean ± standard deviation, number (%) or number/number with data (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; DM: diabetes mellitus; DM_i: diabetes mellitus with insulin; DM_{ni}: diabetes mellitus without insulin; FAST-MI: French registries of Acute ST-elevation and non-ST-elevation myocardial infarction; GRACE: Global Registry of Acute Coronary Events; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction; VKA: vitamin K antagonist.

^a Available in 4169 patients from the 2010 FAST-MI registry.

Table 2 In-hospital outcomes and 1- and 5-year mortality by DM status and occurrence of AHF (pulmonary oedema or cardiogenic shock) during index

	Overall (<i>n</i> = 7839)	No DM, no AHF (<i>n</i> = 5142)	No DM, AHF (<i>n</i> = 546)	DM, no AHF (<i>n</i> = 1716)	DM, AHF (<i>n</i> = 435)	<i>P</i> No DM, no AHF vs No DM, AHF	<i>P</i> DM, no AHF vs DM, AHF
In-hospital outcomes							
AHF	981 (12.5)	0 (0.0)	546 (100)	0 (0.0)	435 (100)	NA	NA
Recurrent MI	118 (1.5)	55 (1.1)	20 (3.7)	26 (1.5)	17 (3.9)	< 0.001	0.001
Stroke	49 (0.6)	22 (0.4)	12 (2.2)	8 (0.5)	7 (1.6)	< 0.001	0.011
Minor or major bleeding	317 (4.0)	174 (3.4)	55 (10.1)	49 (2.9)	39 (9.0)	< 0.001	< 0.001
Minor bleeding	150 (1.9)	93 (1.8)	21 (3.8)	17 (1.0)	19 (4.4)	0.001	< 0.001
Major bleeding	167 (2.1)	81 (1.6)	34 (6.2)	32 (1.9)	20 (4.6)	< 0.001	0.001
AV block	140 (1.8)	66 (1.3)	33 (6.0)	24 (1.4)	17 (3.9)	< 0.001	0.001
Ventricular fibrillation	157 (2.0)	83 (1.6)	39 (7.1)	18 (1.0)	17 (3.9)	< 0.001	< 0.001
Death	332 (4.2)	74 (1.4)	126 (23.1)	41 (2.4)	91 (20.9)	< 0.001	< 0.001
Follow-up							
1-year mortality	879 (11.2)	291 (5.7)	206 (37.7)	197 (11.5)	185 (42.5)	< 0.001	< 0.001
5-year mortality	1918 (24.5)	778 (15.1)	318 (58.2)	521 (30.4)	301 (69.2)	< 0.001	< 0.001

hospital stay.

AHF: acute heart failure; AV, atrioventricular DM: diabetes mellitus; MI: myocardial infarction.

Acute heart failure and Diabetes Mellitus in patients with ACS data from the FAST-MI registries

7,839 patients

4,250 patients with STEMI (54.2%)

3,589 patients with NSTEMI (45.8%)

2,151 patients with DM (27.4%)

629 patients on insulin (8.0%)

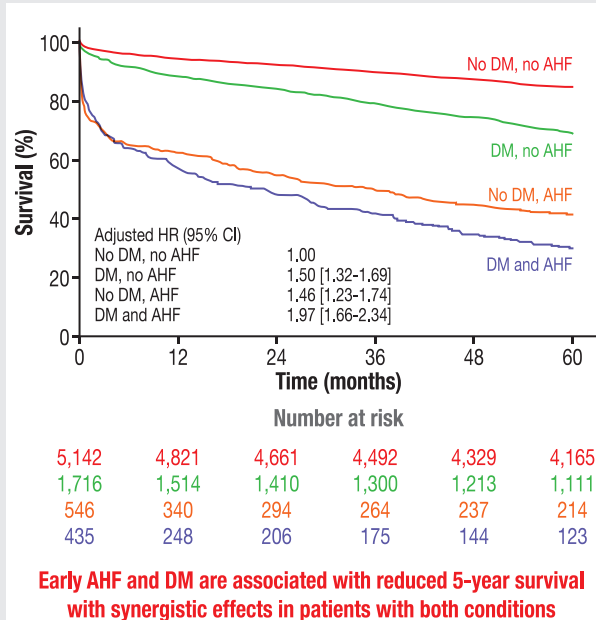
Acute heart failure

AHF : the most frequent in-hospital complication (12.5%)

Risk of AHF is **doubled** in DM patients (20.2% vs 9.6%)

and more the 1.5 times after adjustment

Adjusted OR = 1.66 (95% CI ; 1.43-1.94)



AHF : acute heart failure ; ACS : acute coronary syndrom ; CI : confidence interval ; DM : diabetes mellitus ; HR : hazard ratio ; NSTEMI : non ST-elevation myocardial infarction ; OR ; odds ratio ; STEMI : ST-elevation myocardial infarction

**3,670 patients
(FAST-MI 2005)**

2,354 patients
without DM

STEMI NSTEMI
n=1,317 n=1,037

923 patients
with DM_{ni}

STEMI NSTEMI
n=431 n=492

393 patients
with DM_i

STEMI NSTEMI
n=138 n=255

3,334 patients
without DM

STEMI NSTEMI
n=2,003 n=1,331

**4,169 patients
(FAST-MI 2010)**

599 patients
with DM_{ni}

STEMI NSTEMI
n=283 n=316

236 patients
with DM_i

STEMI NSTEMI
n=78 n=158

5,688 patients
without DM

STEMI NSTEMI
n=3,320 n=2,638

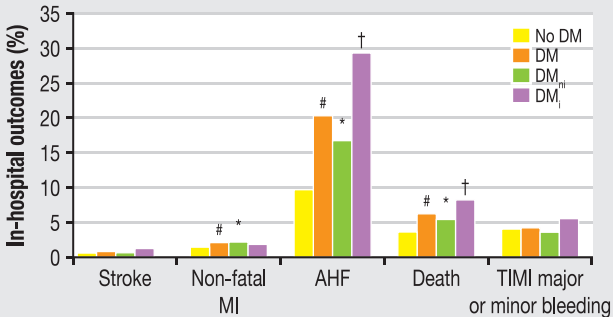
1,522 patients
with DM_{ni}

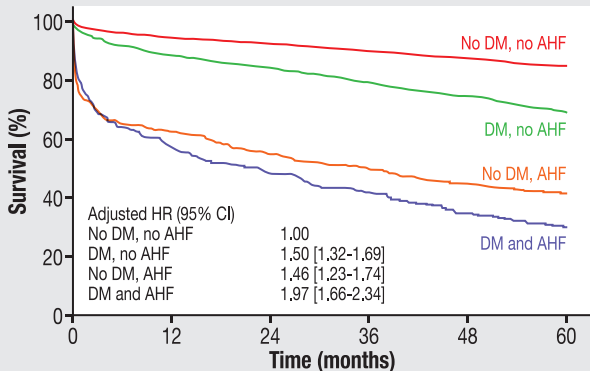
STEMI NSTEMI
n=714 n=808

629 patients
with DM_i

STEMI NSTEMI
n=216 n=413

**7,839 patients
(FAST-MI 2005 and 2010)**





Number at risk

5,142	4,821	4,661	4,492	4,329	4,165
1,716	1,514	1,410	1,300	1,213	1,111
546	340	294	264	237	214
435	248	206	175	144	123