



HAL
open science

Compared impact of diabetes on the risk of heart failure from acute myocardial infarction to chronic coronary artery disease

Gilles Lemesle, Etienne Puymirat, Laurent Bonello, Tabassome Simon, Philippe-Gabriel Steg, Jean Ferrières, François Schiele, Laurent Fauchier, Patrick Henry, Guillaume Schurtz, et al.

► To cite this version:

Gilles Lemesle, Etienne Puymirat, Laurent Bonello, Tabassome Simon, Philippe-Gabriel Steg, et al. Compared impact of diabetes on the risk of heart failure from acute myocardial infarction to chronic coronary artery disease. *Diabetes & Metabolism*, 2022, 48 (1), pp.101265. 10.1016/j.diabet.2021.101265 . hal-04277230

HAL Id: hal-04277230

<https://hal.science/hal-04277230v1>

Submitted on 5 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Compared Impact of Diabetes on the Risk of Heart Failure from Acute Myocardial Infarction to Chronic Coronary Artery Disease

Short title: Diabetes in CAD and risk of HF

First author: Pr. Gilles Lemesle, MD-PhD

List of Authors:

Gilles Lemesle, MD* ; Etienne Puymirat, MD† ; Laurent Bonello, MD‡ ; Tabassome Simon, MD§ ; Philippe-Gabriel Steg, MD|| ; Jean Ferrières, MD¶ ; François Schiele, MD# ; Laurent Fauchier, MD** ; Patrick Henry, MD†† ; Guillaume Schurtz, MD‡‡ ; Sandro Ninni, MD* ; Nicolas Lamblin, MD§§ ; Christophe Bauters, MD§§ ; Nicolas Danchin, MD†.

Institutions:

* Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France. Univ. Lille, F-59000, France. Institut Pasteur of Lille, Inserm U1011, F-59000 Lille, France. FACT (French Alliance for Cardiovascular Trials), F-75000 Paris, France

† Department of Cardiology, Hôpital Européen Georges Pompidou, AP-HP, University of Paris, and FACT (French Alliance for Cardiovascular Trials), Paris, France

‡ Aix-Marseille Univ, Intensive care unit, Department of Cardiology, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Marseille, France ; Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), Marseille, France ; Centre for CardioVascular and Nutrition research (C2VN), INSERM 1263, INRA 1260, Marseille, France

§ Department of Pharmacology and URCEST, Hôpital St Antoine, University of Paris Sorbonne, and FACT (French Alliance for Cardiovascular Trials), Paris, France

|| Department of Cardiology, Hôpital Bichat, AP-HP, University of Paris, and FACT (French Alliance for Cardiovascular Trials), Paris, France

¶ Department of Cardiology, Rangueil hospital, 31400 Toulouse, France

Department of Cardiology, university hospital Jean-Minjoz, 25000 Besançon, France

** Department of Cardiology, CHU de Trousseau, University François-Rabelais, 37170 Chambray-lès-Tours, France

†† Cardiology Department, APHP, Lariboisière Hospital, Paris, France. University of Paris, Paris, France

‡‡ Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France

§§ Heart and Lung Institute, University hospital of Lille, F-59000 Lille, France. Univ. Lille, F-59000, France. Institut Pasteur of Lille, Inserm U1167, F-59000 Lille, France

Address for correspondence: Pr Gilles Lemesle

ServiceUSIC et Centre Hémodynamique , Institut Cœur Poumon, CHU de Lille
59037 Lille Cedex, France

gilles_lemesle@yahoo.fr

Phone +33 320445330

Fax +33 320444898

ABSTRACT

Aim. - We attempted to describe the risk of heart failure (HF) occurrence according to diabetes mellitus (DM) status in patients with coronary artery disease (CAD) over time, from acute myocardial infarction (MI) to the chronic stable phase.

Methods. - For the acute and subacute MI phases, we analysed the FAST-MI cohort restricted to patients without history of HF (n=12,473). The analysis on 1-year outcomes after MI was further restricted to patients who were discharged alive and without history of HF and/or HF symptoms during the index hospitalisation for MI (n=9,181). To analyse the chronic phase, we analysed the CORONOR cohort restricted to patients without history of HF (n=3,871). The primary endpoint was HF occurrence according to DM status. We also analysed the composite of all-cause death or HF.

Results. – Killip-Kimball class \geq II during the index MI hospitalisation was more frequent in DM patients compared to non-DM patients (29% vs. 15.3%, adjusted OR=1.60). At one year after MI, hospitalisation for HF was more frequent in DM patients (3.3% vs. 1.2%, adjusted HR=1.73). At the chronic phase (5-year outcomes), hospitalisation for HF was more frequent in DM patients (8.5% vs. 4.3%, adjusted HR=1.70). Results focusing on the composite endpoint (all-cause death or HF) were consistent.

Conclusion. - DM was associated with a very constant near 2-fold increase in the risk of HF whatever the presentation of CAD. Avoiding the risk of HF occurrence in CAD patients with DM is critical in daily practice and should be a constant life-long endeavour.

Keywords: Coronary artery disease; Diabetes mellitus; Heart failure; Myocardial infarction

ABBREVIATIONS

ACEi/ARB: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

CABG: coronary artery bypass grafting

CAD: coronary artery disease

CI: confidence interval

DM: diabetes mellitus

HF: heart failure

HR: hazard ratio

IQR: interquartile range

LVEF: left ventricle ejection fraction

MI: myocardial infarction

NSTEMI: non-ST-elevation myocardial infarction

OR: odds ratio

STEMI: ST-elevation myocardial infarction

INTRODUCTION

Diabetes mellitus (DM) is associated with an increased risk of heart failure (HF) both in terms of occurrence and severity [1, 2]. In coronary artery disease (CAD) patients, DM is frequent and present in 20% to 30% [3, 4]. In these patients with CAD and DM, progression towards HF is a critical issue in daily practice and is associated with subsequent poor prognosis [5-7].

HF in DM patients may be related to multiple causes and mechanisms: larger myocardial infarction (MI) size related to more diffuse CAD and prothrombotic state [8], deleterious left ventricular remodelling after MI [9], myocardial fibrosis leading to diastolic HF and not well-understood diabetic cardiomyopathy itself [10, 11]. Some of these mechanisms are likely to be preponderant at the acute phase of the disease when others are more implicated at the chronic phase; some are mainly associated with systolic left ventricular dysfunction and others with diastolic dysfunction. Previous studies have focused on each of these mechanisms individually [1, 6, 7, 12-15]. However, no study to our knowledge has tried to analyse the risk of HF development at the different clinical stages of CAD, and to determine whether the risk of developing HF is similarly increased whatever the clinical presentation of CAD.

In the present analysis, using two contemporary large multicentre cohorts, the FAST-MI (French registry of acute ST-elevation or non-ST-elevation myocardial infarction) [4, 16-18] and the CORONOR (*Suivi d'une cohorte de patients CORONariens stables en région NORd-pas-de-Calais*) registries [3], we analysed the risk of HF occurrence according to DM status in CAD patients during the acute phase of MI, during the subacute phase (i.e. within the first year following MI), and during the chronic, stable, phase of the disease.

MATERIAL AND METHODS

Study populations

For the purpose of this study, two populations emanating from real-life registries were used: the FAST-MI and the CORONOR cohorts. The FAST-MI cohort was used to analyse the impact of DM on HF occurrence during the acute phase and within the first year after MI. The CORONOR cohort was used to analyse the impact of DM on HF occurrence in outpatients with stable chronic CAD (at chronological distance from any acute coronary event).

FAST-MI cohort:

Three nationwide French registries were conducted five years apart from 2005 to 2015: FAST-MI 2005 (NCT00673036) [16], FAST-MI 2010 (NCT01237418) [17] and FAST-MI 2015 (NCT02566200) [18]. Methods used for these registries have been previously published [4]. Briefly, their primary objectives were to evaluate the characteristics, management, and outcomes of MI patients, as seen in routine clinical practice, on a country-wide scale. All three registries consecutively included patients with MI admitted to a coronary or intensive care unit within 48 hours of symptom onset during a 1-month period. MI was defined by increased levels of cardiac biomarkers (troponins, creatine kinase or creatine kinase myocardial band) together with either compatible symptoms or electrocardiogram (ECG) changes. Patients who died soon after admission and for whom cardiac markers were not measured were included if they had signs or symptoms associated with typical ST-segment changes. Exclusion criteria were: *i*) refusal to participate; *ii*) iatrogenic MI, defined as occurring within 48 hours of any therapeutic procedure; and *iii*) MI diagnosis invalidated in favour of another diagnosis. ST-elevation MI (STEMI) was diagnosed when ST-elevation ≥ 1 mm was seen in at least two contiguous leads in any location on the index or qualifying

ECG, or when presumed new left bundle branch block or documented new Q waves were observed. In the absence of ST-segment elevation, patients meeting the inclusion criteria were considered to have non-ST-elevation MI (NSTEMI). In the FAST-MI 2005 survey, recruitment was prolonged for one additional month, exclusively for DM patients (explaining the over-representation of DM patients in 2005, compared with the two subsequent surveys). In the FAST-MI 2010 and 2015 surveys, recruitment of all patients meeting the inclusion criteria could be prolonged for up to one additional month in voluntary centres.

For the purpose of this study, the three FAST-MI cohorts were pooled together (n=13,130 patients). As this study was dedicated to analyse new HF episodes in CAD patients, the analysis that focused on acute HF occurrence during the index MI hospitalisation was restricted to patients without history of HF before index MI (Study population 1: n=12,473) ([Figure S1; see supplementary materials associated with this article on line](#)). The analysis that focused on 1-year outcomes was restricted to patients who were discharged alive with no history of HF before index MI and no HF symptoms during the index MI hospitalisation (n=10,043); in addition, the population was further restricted to patients who had complete morbidity follow-up at one year (Study population 2: n=9,181; 91.4%) ([Figure S1; see supplementary materials associated with this article on line](#)).

The protocol of FAST-MI 2005 was reviewed by the Committee for the Protection of Human Subjects (CPP) in Biomedical Research of Saint Antoine University. The protocols of FAST-MI 2010 and FAST-MI 2015 were reviewed and approved by the CPP of Saint Louis University Hospital Paris Ile-de-France IV. Data file collection and storage were approved by the “*Commission Nationale Informatique et Liberté*”. All patients were informed of the nature and aims of the surveys and could request to be excluded; in addition, written consent was obtained for the 2005, 2010, and 2015 surveys.

CORONOR cohort:

As previously published [3], the CORONOR study was a multicentre registry that enrolled 4,184 consecutive outpatients with stable chronic CAD. Patients were enrolled by cardiologists from the French administrative district Nord-Pas-de-Calais during outpatient visits between February 2010 and April 2011 and were followed up to 5 years. Patients were eligible if they presented evidence of CAD defined by at least one of the following criteria: previous MI (>1 year ago), previous coronary revascularisation (>1 year ago), and/or obstruction of $\geq 50\%$ of the luminal diameter of at least one native vessel on coronary angiography. The sole exclusion criterion was hospitalisation for MI or coronary revascularisation within the last year (exclusion of unstable patients).

As this study was dedicated to analyse the occurrence of a new hospitalisation for HF, we focused the present analysis on the 3,871 patients who had no history of hospitalisation for HF at inclusion. Among these patients, 5-year clinical follow-up data were available for 3,785 (98%) patients (Study population 3).

The CORONOR study was approved by the French medical data protection authority and authorised by the “*Commission nationale de l’informatique et des libertés*” for the treatment of personal health data. All patients consented to these studies after being informed in writing of their objectives, the use of their data, together with their right to object, rights of access, and mechanisms for redress. Both registries (FAST-MI and CORONOR) comply with the Declaration of Helsinki.

Definitions and Follow-up

Patients were defined as having DM when treated with oral hypoglycaemic drugs or insulin, or when they had a previous history of elevated (>126 mg/dL) fasting blood glucose on at least two separate occasions in conjunction with ongoing dietary measures in all cohorts.

HF occurrence during the index MI hospitalisation in the FAST-MI cohort was defined as all patients presenting with Killip-Kimball class \geq II at initial presentation or at any time during the hospital stay. HF after discharge was defined as any hospitalisation for HF during follow-up, which was systematically collected in both cohorts. After discharge in the FAST-MI cohort and in the CORONOR registry, hospitalisation for HF was defined as hospitalisation for symptoms of dyspnoea or oedema associated with bilateral rales, elevated venous pressure, or interstitial or alveolar oedema on chest X-ray, or the addition of intravenous diuretics or inotropic medications. Patients who were hospitalised for MI and who had symptoms of HF at admission or during hospitalisation were not adjudicated as hospitalisation for HF because the primary diagnosis was considered to be hospitalisation for MI.

For the FAST-MI cohort, 1-year follow-up was performed by dedicated research technicians who contacted both physicians and patients, after checking the vital status of patients in municipal registers. For all surveys, follow-up was centralised at the French Society of Cardiology, and reported clinical events were adjudicated by a 3-person committee (Nicolas Danchin, MD, Pascal Guéret, MD, Tabassome Simon, MD). One-year clinical follow-up data were available for >99% patients for mortality and for 91.4% of patients for morbid events (i.e. hospitalisation for HF).

For the CORONOR cohort, a 5-year follow-up was performed at outpatient visits with treating cardiologists using a standardised case record form to report clinical events. Five-year clinical follow-up data were available for 3,785 (98%) patients. Missing information was completed by contacting either general practitioners and/or patients themselves. All clinical

events were centrally adjudicated, according to pre-specified definitions, by two investigators blinded to each other. A third investigator joined the adjudication in case of disagreement. For hospitalisations during the follow-up period, hospital records were reviewed for evidence of clinical events. The events reported by the patients were systematically confirmed from the medical reports.

For the present analysis, the primary endpoint was the occurrence of HF as defined above. In order to avoid biases in event reporting (especially missing HF events that led to early death), we also analysed the all-cause death or HF composite as a secondary endpoint.

Statistical analysis

Continuous variables were described as the mean \pm standard deviation (SD) or as median with interquartile range (IQR) as appropriate. Categorical variables were presented as absolute numbers and percentages. Characteristics between the two groups (DM vs. not) were compared with the χ^2 or the Fisher test for categorical variables and with the Student t test for continuous variables as appropriate.

Rates of Killip-Kimball class \geq II and the all-cause death or HF composite during the index MI hospitalisation were compared using logistic regression. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for HF and the all-cause death or HF composite.

Incidences of hospitalisation for HF and of the all-cause death or HF composite (after discharge for the FAST-MI cohort and in the CORONOR cohort) were estimated using the Kaplan-Meier method and compared using the log-rank test. Unadjusted and adjusted hazard ratios (HRs) and 95% CIs were calculated using Cox analyses for HF and the all-cause death or HF composite .

The different models were as follow: *i*) Adjustment for year of inclusion, age, sex, history of hypertension, current smoking, body mass index, type of MI (STEMI vs. NSTEMI), history of MI, history of percutaneous coronary intervention (PCI), history of coronary artery bypass grafting (CABG), history of peripheral artery disease (PAD), history of atrial fibrillation, history of stroke, estimated glomerular filtration rate (eGFR), left ventricle ejection fraction (LVEF), history of chronic obstructive pulmonary disease (COPD), history of cancer, treatment at admission (antiplatelet therapy, statins, betablockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEI/ARB) and diuretics) for the risk of events during the index hospitalisation for MI (FAST-MI cohort, Study population 1); *ii*) Adjustment for year of inclusion, age, sex, history of hypertension, current smoking, body mass index, type of MI (STEMI vs. NSTEMI), history of MI, history of PCI, history of CABG, history of PAD, history of atrial fibrillation, history of stroke, eGFR, LVEF, history of COPD, history of cancer, PCI during the index MI hospitalisation, CABG during the index MI hospitalisation, treatment at discharge (dual antiplatelet therapy, statins, betablockers, ACEI/ARB and diuretics) for the risk of events within the first year after MI (FAST-MI cohort, Study population 2); *iii*) Adjustment for age, sex, history of hypertension, current smoking, history of MI, history of PCI, history of CABG, history of atrial fibrillation, history of stroke, history of PAD, LVEF, eGFR, treatment at inclusion (betablockers, ACEI/ARB and diuretics) for the risk of events during the chronic CAD phase (CORONOR cohort, Study population 3).

All statistical analyses were performed using STATA 14.1 software (STATA Corporation, College Station, Texas, USA) and IBM-SPSS V25.0. Statistical significance was assumed at a *P* value <0.05.

RESULTS

Study populations

Study population 1: The baseline characteristics of the FAST-MI cohort at admission are shown in [Table S1 \(see supplementary materials associated with this article on line\)](#). The proportion of patients with DM was 24.2%. Patients with DM were older than those without, 69.5 vs. 64.2 years, and there were more women among DM patients, 31.7% vs. 27.2% ($P<0.001$). DM patients presented less often with STEMI, 42.3% vs. 57.2%, and showed lower LVEF, 50.7% vs. 52.5% ($P<0.001$). Among the patients with DM, 26.7% received insulin therapy and the mean HbA1c was $7.51\pm 1.54\%$.

Study population 2: The baseline characteristics of the FAST-MI cohort at discharge are detailed in [Table S2 \(see supplementary materials associated with this article on line\)](#). The proportion of patients with DM was 22.1%. Patients with DM were older than those without 67.5 vs. 63.1 years and there were more women among DM patients, 27.4% vs. 25.4% ($P<0.001$). DM patients presented less often with STEMI, 43.4% vs. 57.8%, and showed lower LVEF, 53.4% vs. 54% ($P<0.001$). Patients with DM had less often percutaneous coronary intervention (PCI) during hospital stay, 74.8% vs. 80.3%, and more often coronary bypass surgery (CABG), 4.3% vs. 2.6% ($P<0.001$). There was a wide prescription of dual antiplatelet therapy, statins, ACEI/ARBs, and betablockers. At discharge, diuretics were used in 28% of the patients with DM and 14% of those without ($P<0.001$). Among patients with DM, 31.4% received insulin therapy at discharge and the mean HbA1c was $7.52\pm 1.58\%$.

Study population 3: The baseline characteristics of the CORONOR population are shown in [Table S3 \(see supplementary materials associated with this article on line\)](#). The median time between CAD diagnosis and inclusion into the registry was 6 years (IQR 3 to 10). The proportion of patients with DM was 29.9%. There was no difference in age at inclusion between patients with and without DM, 66.9 vs. 66.4 years. The number of women

was numerically higher in DM patients, 23.5% vs. 20.8% ($P=0.058$). A history of MI was documented in 58% of the DM patients vs. 64.1% in patients without DM ($P<0.001$). Most patients (86.4%) had at least one prior coronary revascularisation procedure prior to inclusion. The mean LVEF was slightly but significantly lower in DM patients 58% vs. 59% ($P=0.0003$). There was a wide prescription of antiplatelet therapy, statins, ACEI/ARBs, and betablockers. Diuretics were used in 38.3% of the patients with DM vs. 22.6% of those without at inclusion ($P<0.001$). Among the patients with DM, 23.9% received insulin therapy at inclusion and the mean HbA1c was $7.25 \pm 1.31\%$.

DM and HF at the acute stage of MI (FAST-MI cohort, Study population 1)

Killip-Kimball class \geq II during the index hospitalisation for MI was present in 29% (n=876 events) of DM patients compared with 15.3% (n=1443 events) of non-DM patients (adjusted OR 1.60; 95% CI 1.43-1.79; $P<0.001$) (Figure 1 and Table I). Results were highly consistent in STEMI and NSTEMI patients (P for interaction = 0.138) and in the three FAST-MI cohorts: FAST-MI 2005, FAST- MI 2010 and FAST-MI 2015 (P for interaction = 0.150).

The all-cause death or HF composite during the index hospitalisation for MI was present in 30.4% of DM patients compared with 16% of non-DM patients (adjusted OR 1.64; 95% CI 1.47-1.83; $P<0.001$) (Figure 1 and Table II). Results were highly consistent in STEMI and NSTEMI patients (P for interaction = 0.134) and in the three FAST-MI cohorts: FAST-MI 2005, FAST- MI 2010 and FAST-MI 2015 (P for interaction = 0.198).

DM and 1-year HF occurrence after MI (FAST-MI cohort, Study population 2)

At 1 year, among the 9,181 patients discharged alive in the FAST-MI cohort, hospitalisation for HF occurred in 3.3% (n=66 events) of the patients with DM compared with 1.2% (n=84 events) of those without DM (adjusted HR 1.73; 95% CI 1.21-2.48, $P=0.003$)

(Figure 2A and Table I). Results were highly consistent in STEMI and NSTEMI patients (P for interaction = 0.132) and in the three FAST-MI cohorts: FAST-MI 2005, FAST- MI 2010 and FAST-MI 2015 (P for interaction = 0.273).

The risk of the all-cause death and hospitalisation for HF composite occurred in 9.6% of the patients with DM compared with 4% of those without DM (adjusted HR 1.71; 95% CI 1.41-2.08, $P < 0.001$) (Figure 2B and Table II). Results were highly consistent in STEMI and NSTEMI patients (P for interaction = 0.371) and in the three FAST-MI cohorts: FAST-MI 2005, FAST- MI 2010 and FAST-MI 2015 (P for interaction = 0.401).

DM and Incidence HF in patients with stable chronic CAD (CORONOR cohort, Study population 3)

Among the 3,785 patients included in the CORONOR registry without history of HF at inclusion, hospitalisation for HF occurred in 8.5% (n=96 events) of the patients with DM compared with 4.3% (n=115 events) of those without at 5 years (adjusted HR 1.70; 95% CI 1.25-2.29; $P = 0.001$) (Figure 3A and Table I). Results were highly consistent in patients with history of MI and in those without (P for interaction = 0.546).

The risk of the all-cause death and hospitalisation for HF composite occurred in 22.1% of the patients with DM compared with 15% of those without DM (adjusted HR 1.53; 95% CI 1.28-1.82; $P < 0.001$) (Figure 3B and Table II). Results were highly consistent in patients with history of MI and in those without (P for interaction = 0.386).

DISCUSSION

It is well established that occurrence of HF is associated with increased mortality over time, and this does also pertain to CAD patients [5, 19-22]. In addition, it has been recently suggested that, even in CAD patients, HF has become the most common cause of

cardiovascular death (i.e. before recurrent MI, stroke, or other atherosclerosis-related causes of death), because of improved management of atherosclerosis [3]. It is therefore critical to identify which CAD patients are at higher risk of HF and to better understand the pathogenesis of HF occurrence in these patients.

The present study from two large multicentre French cohorts [3, 4, 16-18] confirms previous findings [1, 6, 7, 12-15] and shows that, whatever the stage of CAD (acute phase of MI, early months following MI, or stable chronic phase), patients with DM have a constant 70% increased risk of developing HF compared with non-DM patients. In other words, no period showed a higher relative risk of HF occurrence as compared to another, although the absolute risk was higher at the acute stage. This risk was even higher in patients treated with insulin: a fact that may be more related to a longer duration of diabetes exposure, which is commonly observed in these patients, although a direct harmful effect of insulin by itself could not completely be excluded with our design. Therefore, it appears that the prevention of HF occurrence in CAD patients with DM is, first, critical in daily practice, and second, should be a constant life-long endeavour.

Although previous studies have shown an increased risk of developing HF in CAD patients with DM [1, 6, 7, 12-15], to our knowledge, our study is the first to assess the temporality of HF occurrence, in order to apprehend the relative impact of DM on the different mechanisms of HF in CAD patients. This aspect may be of major interest when it comes to initiating or adapting treatments in these patients. Therefore, it may be relevant to identify whether DM impacts more one mechanism of HF over another in CAD patients. In previous studies, DM has been associated with a higher rate of HF at the acute phase of MI. Larger MI size related to more diffuse CAD at diagnosis, atypical chest pain or absence of pain leading to delayed management, and a specific prothrombotic state in DM patients may all increase the risk of HF occurrence in these circumstances [8]. In this context, early

coronary revascularisation and intensive antithrombotic therapies using new P2Y₁₂-receptor inhibitors have shown clinical benefit, in DM as in non-DM patients. Following MI, DM is also associated with a higher risk of improper left ventricular remodelling, which may also increase the risk of subsequent hospitalisation for HF [9]. Early initiation of specific HF treatments (betablockers, ACEi/ARB, mineralocorticoid receptor antagonists ...) is likely to be of major importance particularly in this sub-population. These improvements in patient care, however, seem not to erase the excess risk of HF in patients with DM. As an example, DM was still associated with a 38% excess risk of cardiovascular death or hospitalisation for HF in the recent PARADIGM-HF trial [23]. Finally, myocardial fibrosis and left ventricle rigidity have also been associated with diastolic HF [10, 11]. Whatever the underlying mechanisms leading to clinical HF, our results show that DM impacts HF occurrence to the same extent at all time points of the disease.

Thus, prevention of HF in DM patients is of particular importance as it is a common complication of CAD at all stages, and carries a much poorer prognosis. Anti-diabetic medications may have different impacts on HF occurrence. Glitazones have shown to increase the risk of HF [24]. The role of other anti-diabetic drugs such as metformin, insulin, DPP-4 inhibitors or glucagonlike peptide-1 (GLP-1) agonist, is unclear [25], while sodium glucose co-transporter type 2 (SGLT-2) inhibitors prevent HF in DM as in non-DM patients [26-28]. The mechanism of action of SGLT-2 inhibitors remains however uncertain. SGLT-2 inhibitors might have a greater preventative impact during the chronic phase of CAD, rather than in acute situations. Recently, Singh et al. showed that dapagliflozin has no significant impact on left ventricular remodelling early after MI [9]. Of note, a clinical trial investigating initiation of empagliflozin immediately after MI with reduced LVEF is currently recruiting patients (the EMPACT-MI study NCT04509674) in order to assess this specific point. In addition, aside from considerations in HF prevention, GLP-1 agonists have shown to reduce

atherosclerotic events in DM patients, which is also a critical point in CAD patients with DM. Thus, a combination of GLP-1 agonists and SGLT-2 inhibitors in CAD patients with DM may be a highly relevant combination in the near future.

Strengths and limitations

In order to assess the real impact of DM on HF development over time in CAD patients, we excluded at each time point of the study all patients with a history of previous HF. Our goal was indeed to assess the independent role of DM on new-onset HF. Some limitations have to be acknowledged. First, the lack of LVEF assessment at the time of HF occurrence limits the interpretation of the mechanism (systolic vs. diastolic) of left ventricular dysfunction. Second, our results emanate from two different multicentre French cohorts of patients and not from a single cohort. This, however, provided a unique opportunity to concomitantly analyse the entire spectrum of HF during the time course of CAD, including chronic stable CAD, which to the best of our knowledge, had not been done in the past.

CONCLUSIONS

In CAD patients, DM is associated with a remarkably constant 70% increase in the risk of developing HF, whatever the stage of the disease, from acute situations such as acute MI, to the post-MI subacute period, and up to the chronic phase of the disease. Avoiding HF occurrence should therefore be a permanent objective in everyday management of CAD patients with DM, with the optimal use of conventional therapy as well as new medications for HF prevention.

AUTHOR CONTRIBUTION

All authors have actively contributed to the manuscript as followed:

- 1) conception and design or analysis and interpretation of data, or both: GL, CB and ND
- 2) drafting of the manuscript or revising it critically for important intellectual content: EP, LB, TS, PGS, JF, FS, LF, PH, GS, SN, and NL
- 3) final approval of the manuscript submitted: GL, CB and ND.

CONFLICT OF INTEREST

None of the authors has any relationship with industry and financial associations that might pose a conflict of interest in direct connection with the submitted article.

FUNDING STATEMENTS

The French Society of Cardiology received grants for supporting the FAST-MI program from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, MSD, Pfizer, and Sanofi. None of the companies had a role in the design and conduct of the study, data collection and management. They were not involved in the analysis and interpretation of the data, nor in the preparation, review, or approval of the manuscript. The CORONOR study was supported by the *Fédération Française de Cardiologie* (Paris, France).

ACKNOWLEDGMENTS

None

Appendix supplementary material

Supplementary materials (Fig. S1 and Tables S1-S2-S3) associated with this article can be found at <http://www.sciencedirect.com> at doi . . .

REFERENCES

1. Bauters C, Lamblin N, Mc Fadden EP, Van Belle E, Millaire A, de Groote P. Influence of diabetes mellitus on heart failure risk and outcome. *Cardiovasc Diabetol* 2003; 2:1.
2. De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, Bauters C. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004; 25:656-62.
3. Bauters C, Deneve M, Tricot O, Meurice T, Lamblin N, Investigators C. Prognosis of patients with stable coronary artery disease (from the CORONOR study). *Am J Cardiol* 2014; 113:1142-5.
4. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, *et al.* Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation* 2017; 136:1908-19.
5. Lamblin N, Meurice T, Tricot O, de Groote P, Lemesle G, Bauters C. First hospitalization for heart failure in outpatients with stable coronary artery disease: determinants, role of incident myocardial infarction, and prognosis. *J Card Fail* 2018; 24:815-22.
6. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J* 2004; 148:883-8.
7. Cavender MA, Steg PG, Smith SC Jr., Eagle K, Ohman EM, Goto S, *et al.* Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the reduction of atherothrombosis for continued health (REACH) Registry. *Circulation* 2015; 132:923-31.
8. Lemesle G, Bauters A, Bauters C. Antithrombotic therapy in diabetic patients with coronary artery disease. *Panminerva Med* 2015; 57:87-99.
9. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, *et al.* Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: The REFORM Trial. *Diabetes Care* 2020;43(6):1356-9.

10. Mordi IR, Tee A, Palmer CN, McCrimmon RJ, Doney ASF, Lang CC. Microvascular disease and heart failure with reduced and preserved ejection fraction in type 2 diabetes. *ESC Heart Fail* 2020;7:1168-77.
11. Maack C, Lehrke M, Backs J, Heinzl FR, Hulot JS, Marx N, *et al.* Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J* 2018; 39:4243-54.
12. Parizo J, Mahaffey KW. Diabetes and heart failure post-acute myocardial infarction: Important associations and need for evidence-based interventions. *Eur J Prev Cardiol* 2020; 27:1887-9.
13. Ritsinger V, Nystrom T, Saleh N, Lagerqvist B, Norhammar A. Heart failure is a common complication after acute myocardial infarction in patients with diabetes: A nationwide study in the SWEDEHEART registry. *Eur J Prev Cardiol* 2020; 27:1890-901.
14. Takeji Y, Shiomi H, Morimoto T, Furukawa Y, Ehara N, Nakagawa Y, *et al.* Diabetes mellitus and long-term risk for heart failure after coronary revascularization. *Circ J* 2020; 84:471-8.
15. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study. *Diabetes Care* 2010; 33:2084-9.
16. Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. *Arch Mal Coeur Vaiss* 2007; 100:524-34.
17. Hanssen M, Cottin Y, Khalife K, Hammer L, Goldstein P, Puymirat E, *et al.* French registry on acute st-elevation and non st-elevation myocardial infarction 2010. FAST-MI 2010. *Heart* 2012; 98:699-705.
18. Belle L, Cayla G, Cottin Y, Coste P, Khalife K, Labeque JN, *et al.* French registry on acute st-elevation and non-st-elevation myocardial infarction 2015 (FAST-MI 2015). Design and baseline data. *Arch Cardiovasc Dis* 2017; 110:366-78.
19. Parma Z, Jasilek A, Greenlaw N, Ferrari R, Ford I, Fox K, *et al.* Incident heart failure in outpatients with chronic coronary syndrome: results from the international prospective CLARIFY registry. *Eur J Heart Fail* 2020;22: 804-12.

20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37:2129-200.
21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr., Colvin MM, *et al.* 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. *Circulation* 2017; 136:e137-e161.
22. Bahit MC, Kochar A, Granger CB. Post-Myocardial Infarction Heart Failure. *JACC Heart Fail* 2018; 6(3):179-86.
23. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, *et al.* Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. *Circ Heart Fail* 2016; 9:e002560.
24. Gilbert RE, Krum H: Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. *Lancet* 2015; 385:2107-17.
25. Cattadori G, Pantanetti P, Ambrosio G. Glucose-lowering drugs and heart failure: implications of recent cardiovascular outcome trials in type 2 diabetes. *Diabetes Res Clin Pract* 2019; 157:107835.
26. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, *et al.* Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381:1995-2008.
27. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377:2099.
28. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373:2117-28.

FIGURE LEGENDS

Figure 1. Risk of events in Study population 1 (during the index MI hospitalisation).

Impact of DM status on the risk of HF and the all-cause death or HF composite during the index hospitalisation for MI in the FAST-MI cohort (Study population 1): comparison of DM patients and non-DM patients

DM = diabetes mellitus, HF = heart failure

Figure 2. Risk of events in Study population 2 (within the first year after MI).

Impact of DM status on the risk of HF and the all-cause death or HF composite within the first year after MI in the FAST-MI cohort (Study population 2). Kaplan-Meier curves.

A. Risk of HF in DM patients and non-DM patients

B. Risk of the all-cause death or HF composite in DM patients and non-DM patients

DM = diabetes mellitus

Figure 3. Risk of events in Study population 3 (5-year follow-up).

Impact of DM status on the risk of HF and the all-cause death or HF composite in stable chronic CAD patients in the CORONOR cohort at 5 years (Study population 3). Kaplan-Meier curves.

A. Risk of HF in DM patients and non-DM patients

B. Risk of the all-cause death or HF composite in DM patients and non-DM patients

DM = diabetes mellitus

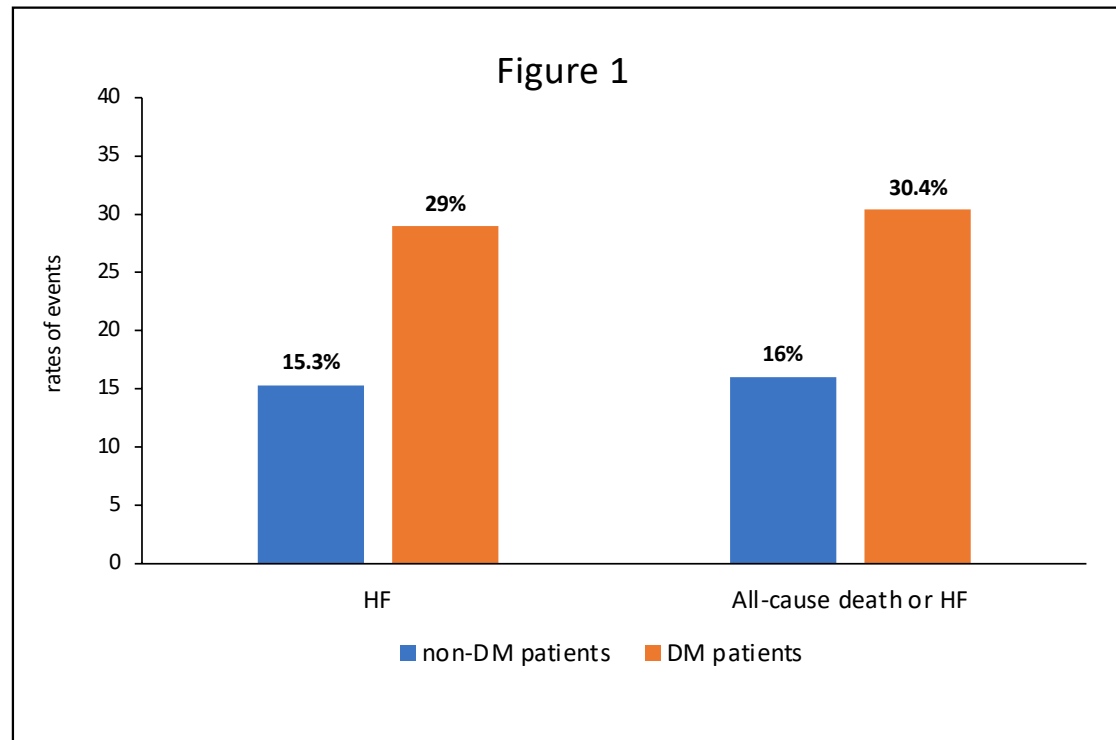
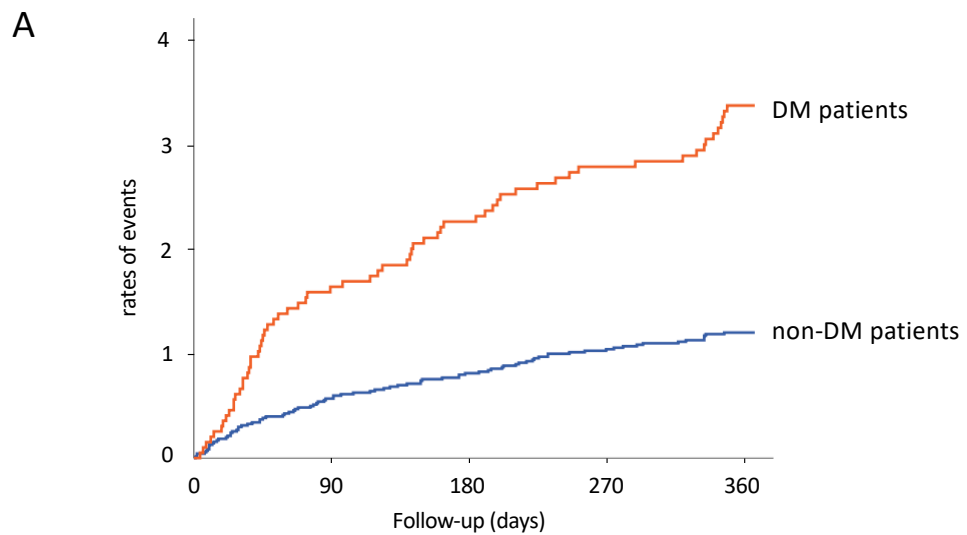
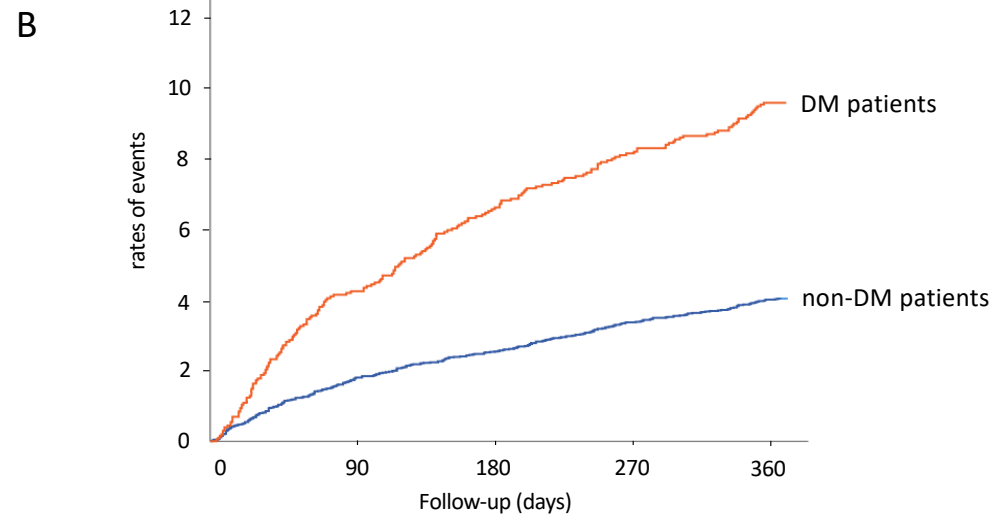


Figure 2



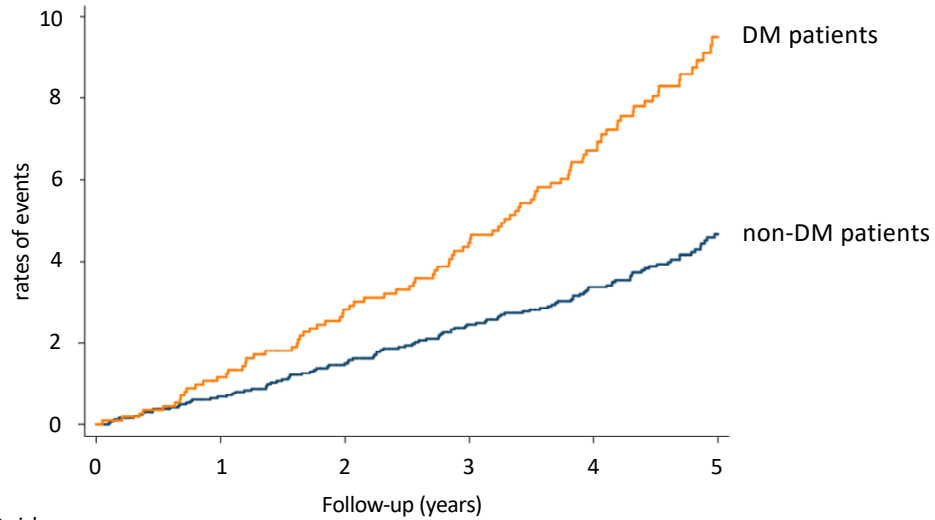
Numbers at risk					
No DM	7157	6967	6931	6886	6742
DM	2024	1907	1872	1844	1803



Numbers at risk					
No DM	7157	7033	6976	6915	6868
DM	2024	1939	1892	1859	1831

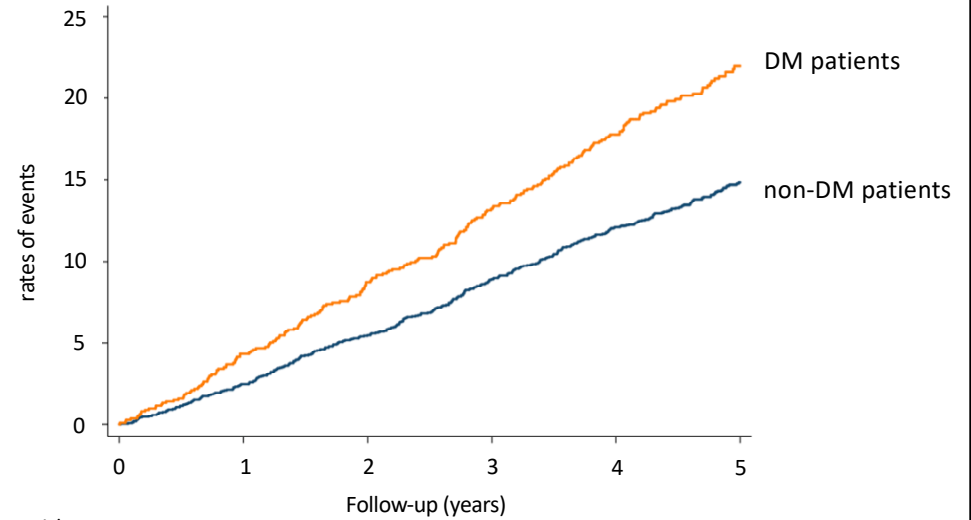
Figure 3

A



Numbers at risk		Follow-up (years)					
	0	1	2	3	4	5	
No DM	2650	2584	2505	2414	2283	1131	
DM	1135	1086	1036	985	921	423	

B



Numbers at risk		Follow-up (years)					
	0	1	2	3	4	5	
No DM	2650	2584	2505	2414	2283	1131	
DM	1135	1086	1036	985	921	423	

Table I. Association between DM and the risk of HF occurrence in CAD patients.

Relative risks (OR and HR) are presented as DM vs. non-DM patients.

Risk of HF during the index MI hospitalization	OR [95% CI]	P value
The FAST-MI cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	2.26 [2.05-2.49]	< 0.001
Patients with diabetes without insulin therapy	1.91 [1.71-2.14]	< 0.001
Patients with diabetes under insulin therapy	3.37 [2.90-3.92]	< 0.001
<i>Adjusted^a</i>		
Patients without diabetes	Reference	-
Patients with diabetes	1.60 [1.43-1.79]	< 0.001
Patients with diabetes without insulin therapy	1.46 [1.29-1.65]	< 0.001
Patients with diabetes under insulin therapy	2.05 [1.72-2.45]	< 0.001
Risk of hospitalization for HF within the first year after MI	HR [95% CI]	P value
The FAST-MI cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	2.83 [2.05-3.92]	< 0.001
Patients with diabetes without insulin therapy	1.68 [1.09-2.60]	0.019
Patients with diabetes under insulin therapy	5.52 [3.76-8.10]	< 0.001
<i>Adjusted^b</i>		
Patients without diabetes	Reference	-
Patients with diabetes	1.73 [1.21-2.48]	0.023
Patients with diabetes without insulin therapy	1.14 [0.73 -1.77]	0.571
Patients with diabetes under insulin therapy	2.56 [1.69-3.88]	< 0.001
Risk of hospitalization for HF in stable CAD outpatients	HR [95% CI]	P value
The CORONOR cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	2.04 [1.56-2.68]	< 0.001
Patients with diabetes without insulin therapy	1.78 [1.32-2.42]	< 0.001
Patients with diabetes under insulin therapy	2.95 [1.98-4.38]	< 0.001
<i>Adjusted^c</i>		
Patients without diabetes	Reference	-

Patients with diabetes	1.70 [1.25-2.29]	0.001
Patients with diabetes without insulin therapy	1.52 [1.09-2.13]	0.014
Patients with diabetes under insulin therapy	2.22 [1.43-3.44]	< 0.001

OR = odds ratio; HR = hazard ratio; CI = confidence interval; HF = heart failure; MI = myocardial infarction; CAD = coronary artery disease

^a Adjusted for year of inclusion, age, sex, history of hypertension, current smoking, body mass index, type of MI (STEMI vs. NSTEMI), history of MI, history of PCI, history of CABG, history of PAD, history of atrial fibrillation, history of stroke, eGFR, LVEF, history of COPD, history of cancer, treatment at admission (antiplatelet therapy, statins, betablockers, ACEI/ARB and diuretics).

^b Adjusted for year of inclusion, age, sex, history of hypertension, current smoking, body mass index, type of MI (STEMI vs. NSTEMI), history of MI, history of PCI, history of CABG, history of PAD, history of atrial fibrillation, history of stroke, eGFR, LVEF, history of COPD, history of cancer, PCI during the index MI hospitalization, CABG during the index MI hospitalization, treatment at discharge (dual antiplatelet therapy, statins, betablockers, ACEI/ARB and diuretics).

^c Adjusted for age, sex, history of hypertension, current smoking, history of MI, history of PCI, history of CABG, history of atrial fibrillation, history of stroke, history of PAD, LVEF, eGFR, treatment at inclusion (betablockers, ACEI/ARB and diuretics).

Table II. Association between DM and the risk of the composite of all-cause death or HF in CAD patients.

Relative risks (OR and HR) are presented as DM vs. non-DM patients.

Risk of the composite death or HF during the index MI hospitalization	OR [95% CI]	P value
The FAST-MI cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	2.29 [2.09-2.52]	< 0.001
Patients with diabetes without insulin therapy	1.94 [1.74-2.17]	< 0.001
Patients with diabetes under insulin therapy	3.41 [2.93-3.96]	< 0.001
<i>Adjusted^a</i>		
Patients without diabetes	Reference	-
Patients with diabetes	1.64 [1.47-1.83]	< 0.001
Patients with diabetes without insulin therapy	1.51 [1.33-1.70]	< 0.001
Patients with diabetes under insulin therapy	2.07 [1.73-2.47]	< 0.001
Risk of the composite death or HF within the first year after MI	HR [95% CI]	P value
The FAST-MI cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	2.45 [2.04-2.93]	< 0.001
Patients with diabetes without insulin therapy	1.76 [1.40-2.21]	< 0.001
Patients with diabetes under insulin therapy	4.02 [3.20-5.07]	< 0.001
<i>Adjusted^b</i>		
Patients without diabetes	Reference	-
Patients with diabetes	1.71 [1.41-2.08]	< 0.001
Patients with diabetes without insulin therapy	1.39 [1.09-1.76]	0.007
Patients with diabetes under insulin therapy	2.30 [1.79-2.96]	< 0.001
Risk of the composite death or HF in stable CAD outpatients	HR [95% CI]	P value
The CORONOR cohort		
<i>Unadjusted</i>		
Patients without diabetes	Reference	-
Patients with diabetes	1.54 [1.31-1.80]	< 0.001
Patients with diabetes without insulin therapy	1.38 [1.15-1.64]	< 0.001
Patients with diabetes under insulin therapy	2.09 [1.64-2.67]	< 0.001

Adjusted^c

Patients without diabetes	Reference	-
Patients with diabetes	1.53 [1.28-1.82]	< 0.001
Patients with diabetes without insulin therapy	1.39 [1.14-1.69]	0.001
Patients with diabetes under insulin therapy	1.97 [1.51-2.58]	< 0.001

HF = heart failure; MI = myocardial infraction; CAD = coronary artery disease

^a year of inclusion, type of MI (STEMI vs. NSTEMI), age, sex, history of hypertension, current smoking, history of MI, history of PCI, history of CABG, history of atrial fibrillation, history of stroke, history of PAD, eGFR, previous use of betablockers, ACEI/ARB and diuretics.

^b Adjusted for year of inclusion, type of MI (STEMI vs. NSTEMI), age, sex, history of hypertension, current smoking, history of MI, history of PCI, history of CABG, history of atrial fibrillation, history of stroke, history of PAD, LVEF, eGFR, previous use of betablockers, ACEI/ARB and diuretics, PCI during the index MI hospitalization, CABG during the index MI hospitalization.

^c Adjusted for age, sex, history of hypertension, current smoking, history of MI, history of PCI, history of CABG, history of atrial fibrillation, history of stroke, history of PAD, LVEF, eGFR, previous use of betablockers, ACEI/ARB and diuretics.