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Impact of gender on relative rates of cardiovascular events in patients with diabetes

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Short title: Diabetes, gender and cardiovascular events

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Abstract

Aim. – To investigate whether diabetes confers higher relative risks of cardiovascular events in women compared with men using contemporary data and also whether such gender-differences are dependent on age.

Methods. – All patients discharged from French hospitals in 2013 with at least 5 years of follow-up and no history of major adverse cardiovascular events including heart failure (MACE-HF; heart failure, myocardial infarction, ischaemic stroke, cardiovascular death) were identified and categorized by diabetes status. Overall and age-stratified incidence rates, hazard ratios (HRs) and women-to-men ratios (WMRs) for MACE-HF leading to hospitalization were also calculated. Adjustments were then made for age and baseline characteristics according to cardiovascular risk factors and non-cardiovascular comorbidities.

Results. – The study included 2,953,816 subjects, among whom 349,928 (11.9%) had diabetes. Of those with diabetes, the absolute rate of MACE-HF was higher in men than in women (96 *vs* 66 per 1000 person-years); corresponding absolute rates in men and women without diabetes were 44 *vs* 27 per 1000 person-years. Comparing those with and without diabetes, women had a higher unadjusted HR of MACE-HF (2.45, 95% CI: 2.42–2.47) than men (2.15, 95% CI: 2.14–2.17), with an adjusted WMR of 1.13 (95% CI: 1.12–1.15). HRs of MACE-HF related to diabetes were highest in women aged around 45 years and in the youngest men and decreased with advancing age in both these groups. However, HRs were higher in women of all ages > 40 years. After adjustment, this effect was more apparent for myocardial infarction (adjusted WMR: 1.43, 95% CI: 1.38–1.48) than for either ischaemic stroke (adjusted WMR: 1.10, 95% CI: 1.07–1.14) or heart failure (adjusted WMR: 1.13, 95% CI: 1.11–1.14).

Conclusion. – Although men have higher absolute risks of cardiovascular complications, the relative risks of cardiovascular complications associated with diabetes are higher in women than in men.

Keywords: Cardiovascular disease; Diabetes; Heart failure; Myocardial infarction; Gender difference

Abbreviations

WMR, women-to-men ratio; MACE-HF, heart failure, myocardial infarction, ischaemic stroke, cardiovascular death; PMSI, *Programme de Médicalisation des Systèmes d'Information*; IR, incidence rate

Introduction

All-cause mortality risk is almost doubled in patients with diabetes compared with the general population even after adjusting for other risk factors [1]. Cardiovascular diseases are the major component of this excess death risk, and previous large-scale studies have suggested that the proportional increase is higher in women than in men [2,3]. Recent data, however, have challenged this gender-based difference in excess risk, suggesting that the previously observed differences were related to old studies not taking into account the more recent changes in diabetes definition and management strategy [4,5]. It has also been suggested that the excess risk observed in women with diabetes may be related to less optimal cardiovascular risk-factor management, including post-myocardial infarction (MI) secondary prevention [6–8]. Age and gender interactions can also influence gender-based differences in diabetes related risk, as suggested by data showing greater age-related stiffening of the aorta in women compared with men with diabetes and hypertension [9].

To further investigate this topic, the present longitudinal cohort study of a contemporary population was performed to assess whether diabetes confers higher relative rates of cardiovascular events in women than in men, and whether these gender differences also depend on age.

Methods

Study design

The present longitudinal cohort study was based on the French national hospitalization database covering hospital care in the entire French population. Data for all patients admitted to hospitals in France from January to December 2013 with at least 5 years of complete follow-up (or in-hospital death) were collected from the national administrative *Programme de Médicalisation des Systèmes d'Information* (PMSI; French hospital discharge database), which was inspired by the US Medicare system. Through this programme, initially implemented in 2004, all medical activity is recorded in a database, then computerized and rendered anonymous. It includes > 98% (67 million people) of the French population from birth (or immigration) to death (or emigration), regardless of changes in occupation or retirement. The process allows the budget of each hospital in 1546 French healthcare facilities (both public and private) to be determined. Every hospitalization is encoded in a standardized dataset, including information about the patient (age and gender at first hospitalization in 2013) and hospital, length of stay (date of admission, date of discharge, modes of discharge), pathologies and procedures. The routinely collected medical information includes the

principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the *International Classification of Diseases, Tenth Revision* (ICD-10). All medical procedures are recorded according to the French national medical classification system laid out in the *Classification Commune des Actes Médicaux* (CCAM).

The PMSI contains individual anonymized information on every hospitalization that is linked to create a longitudinal record of hospital stays and diagnoses for each patient. A period of 3 years (2010–2013) was used to determine each patient's medical history. This type of longitudinal analysis has been used by others [10] and has previously been used to study patients with cardiovascular conditions [11–14]; the reliability of PMSI data has already been assessed. Medication use was identified from a 1/97 permanent random sample of the complete French nationwide claims database [*Echantillon Généraliste de Bénéficiaires* (EGB), general sample of healthcare beneficiaries]. However, this database is not linked to the PMSI database, which has previously been used to study patients with diabetes in France [15]. In the present study, patients were enrolled using the same inclusion criteria as in the PMSI database (patients seen in 2013 with at least 5 years of follow-up) and were considered as included in a treatment group if they received treatment from a class of drugs for ≥ 60 days within 6 months of enrolment.

The present study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care and ethical approval was not required as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the *Commission Nationale de l'Informatique et des Libertés* (CNIL) and the independent French National Consultative Ethics Committee, which protects human rights in France and ensures that all information is kept confidential and anonymous. Finally, the study was in compliance with the Declaration of Helsinki (authorization number 1897139).

Study population

From 1 January 2013 to 31 December 2013, 3,381,472 adults (aged ≥ 18 years) hospitalized for any reason in French hospitals with ≥ 5 years of complete follow-up (or in-hospital death) were identified. Patients' information (demographics, comorbidities, medical history, events during hospitalization or follow-up) was described based on data collected from hospital records. For each hospital stay, the combined diagnoses at discharge were obtained. Each diagnosis was identified using ICD-10 codes and, because the information was based on codes, there were no missing values. Diabetes was identified by the following ICD-10 codes:

E10, E11, E12, E13, E14. Exclusion criteria were age < 18 years or previous hospitalization for in-hospital cardiovascular death, MI, ischaemic stroke or new-onset heart failure events [major adverse cardiovascular events including heart failure (MACE-HF)] recorded over the 2010–2013 period.

Outcomes

Patients were followed up to 31 December 2019 for the occurrence of outcomes. The aim was to evaluate the incidence of the first MACE-HF events. Endpoints were evaluated with follow-up starting from the date of discharge for the first hospitalization in 2013 to the date of each specific outcome or date of the last report in the absence of an outcome. Information on outcomes during follow-up was obtained by analyzing the PMSI codes for each patient. All-cause death, cardiovascular death, MI (ICD codes I21–I23), ischaemic stroke (ICD code I63) and heart failure (ICD codes I11, I255, I130, I132, I42, I43, I50, J81, R570) were identified according to their respective ICD-10 codes. Mode of death (cardiovascular or non-cardiovascular) was identified based on the main diagnosis during hospitalization that resulted in the in-hospital death. A combined endpoint (cardiovascular death, MI, ischaemic stroke, heart failure) was evaluated for long-term follow-up.

Statistical analysis

Qualitative variables are described as frequency (n) and percentages (%), and quantitative variables as means and standard deviation (SD). Multivariable analyses for clinical outcomes during the entire follow-up in the study groups of interest were performed using a Cox model, with baseline characteristics for age, cardiovascular risk factors (smoking, obesity, hypertension, dyslipidaemia, alcohol-related diagnoses) and non-cardiovascular comorbidities (chronic kidney disease, lung disease, sleep apnoea syndrome, chronic obstructive pulmonary disease, liver disease, gastroesophageal reflux, thyroid disease, inflammatory disease, anaemia, previous cancer, denutrition, cognitive impairment, illicit drug use). The data are reported as incidence rates (IR; events/1000 person-years), hazard ratios (HRs), and women-to-men ratios (WMRs; HRs for women *vs* HRs for men) and 95% confidence intervals (CIs), including unadjusted WMRs (unadjusted HRs for women *vs* unadjusted HRs for men) and adjusted WMRs (adjusted HRs for women *vs* adjusted HRs for men).

All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) and Stata version 12.0 (StataCorp, College Station, TX, USA) software.

Results

The present study identified 2,953,816 patients seen in French hospitals in 2013 with no past history of MACE-HF, including 349,928 people with prevalent diabetes (48% female; Fig. S1; see supplementary materials associated with this article online). Population characteristics at baseline showed that those with diabetes had more comorbidities and treated comorbidities than people without diabetes, whereas the comorbidities and treated comorbidities were similar between men and women irrespective of diabetes status (Table I). However, women with diabetes were slightly younger and less frequently had coronary artery disease than men with diabetes.

Using data for medications of the 1/97 sample of patients from the French healthcare system for those with the same inclusion criteria, patients with diabetes were more frequently treated (around two to three times as often) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, diuretics, antiarrhythmic agents, antithrombotic therapy or statins than patients without diabetes (Table II). Among patients with diabetes in our dataset, women were less often treated with these medications than men except for diuretics and calcium-channel blockers.

Over the 13.6 million person-years of follow-up, 528,617 patients with new-onset MACE-HF events were identified, including 80,006 with MI, 407,600 with heart failure, 87,112 with ischaemic stroke and 106,276 cardiovascular deaths. In addition, IRs of MACE-HF increased with advancing age in patients with both type 1 (T1D) and type 2 diabetes (T2D) (Fig. 1).

In women with diabetes, 47,026 experienced MACE-HF events over a total of 717,000 person-years of follow-up, equivalent to an IR of 66/1000 person-years. In women without diabetes, 186,445 had MACE-HF events over 7.0 million person-years of follow-up, yielding an IR of 27/1000 person-years (Table S1; see supplementary materials associated with this article online). In addition, IRs for MACE-HF were higher in men than in women irrespective of diabetes status and age (Fig. 1). Therefore, the HR for women (diabetes/no diabetes) was 2.45 (95% CI: 2.42–2.47), and the corresponding HR for men was 2.15 (95% CI: 2.14–2.17), with IRs of 96/1000 person-years in men with diabetes and 44/1000 person-years in men without diabetes. The HR for women was significantly higher than the HR for men, as confirmed by the WMR: unadjusted WMR (HR women *vs* HR men): 1.14, 95% CI: 1.13–1.16 (Fig. 2); and adjusted WMR: 1.13, 95% CI: 1.12–1.15. Results were similar for a sensitivity analysis limited to patients with T2D compared with those without diabetes: adjusted WMR for MACE-HF: 1.12, 95% CI: 1.11–1.14.

In fact, such a relationship was seen for all components of MACE-HF events, but was more

evident for MI, with an adjusted WMR of 1.07 (95% CI: 1.04–1.11) for cardiovascular death, an adjusted WMR of 1.43 (95% CI: 1.38–1.48) for MI, an adjusted WMR of 1.10 (95% CI: 1.07–1.14) for ischaemic stroke and an adjusted WMR of 1.13 (95% CI: 1.11–1.14) for heart failure (Table III, Tables S1–S2, Figs. S2–S3; see supplementary materials associated with this article online). In addition, the HR (diabetes/no diabetes) for all MACE-HF outcomes was highest in women aged around 45 years and decreased with advancing age and was also highest in the youngest men and decreased with advancing age. Moreover, the HRs for MACE-HF were higher in women than in men across all ages > 40 years, with the highest WMRs observed between ages 45 and 70 years (Fig. 3, Figs. S4–S7; see supplementary materials associated with this article online).

Discussion

Our large-scale longitudinal cohort study investigating gender differences in the incidence of cardiovascular events in patients with diabetes confirms previous reports of a higher incidence in women with diabetes compared with women without diabetes [3,6,16]. All components of the MACE-HF composite outcome were significantly increased in women with *vs* without diabetes in our contemporary population. Analysis of the overall population also found an excess risk of early cardiovascular events in men with diabetes, although the HRs clearly indicated a significantly higher relative risk (RR) of cardiovascular events in women with diabetes *vs* women without diabetes compared with men. These results differ from the retrospective study performed in England between 2006 and 2013 of a cohort of patients with type 2 diabetes that found no significant gender disparities in cardiovascular risk associated with diabetes [4]. This difference might be explained by differences in population characteristics: the present French cohort of patients with diabetes was identified at the time of hospitalization, were older in age and followed-up for longer. Moreover, our large-scale study had sufficient statistical power to reveal that these gender differences were found with each separate component of the composite cardiovascular outcome used in our analyses.

In our contemporary study, age-stratified analysis confirmed that the excess risk observed in women was mostly in younger and middle-aged patients, as was also previously reported in an older-aged registry from Sweden [17]. Also, the WMR abruptly increased after age 40 years and reached a plateau of 1.4 at age 50 years, then continued up to age 65 years before sliding down to 1.1 at age 80. These data are in keeping with observations from a smaller analysis carried out in Denmark, and support the implementation of intensive preventative and therapeutic interventions in younger people [17,18]. Among the components of MACE-

HF in our study, MI showed the highest WMR, peaking at 1.43 after multivariable adjustment. This excess MI risk in women with diabetes had previously been reported [19–22]. The recently published ADVANCE-ON study, a post-trial follow-up of Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), investigated gender-specific associations between cardiovascular risk factors and MI in patients with T2D, and showed that smoking, higher systolic blood pressure (SBP) and longer duration of diabetes might explain a greater RR of MI in women with diabetes compared with men with diabetes [23]. By contrast, it was recently reported that every 1% increase in HbA1c value could be associated with a similar higher risk of MI in both women and men [24].

Gender differences in risk may be the result of the complex interplay between hormonal homoeostasis, energy imbalance, ectopic fat distribution and psychosocial factors [25]. Our present data also found a significantly higher WMR for heart failure, placing it second after MI. Haas et al. [26] reported that women with well-controlled diabetes might experience more coronary microvascular dysfunction leading to more severe diastolic function than in men with diabetes. The authors also suggested that greater aldosterone responsiveness in women with diabetes could be the mechanism behind this gender-based effect and hypothesized that it might be improved by mineralocorticoid blockade. Of note and interestingly, it was recently suggested that sodium–glucose cotransporter type-2 (SGLT2) inhibition might provide similar protection against vascular risks, heart failure and death, but also similar risks of serious adverse events, in both women and men with T2D [27].

In fact, diabetes could abrogate the protective effect of female gender against cardiovascular complications across all ages [28]. Steinberg et al. [29] found that diabetes was associated with impairment of nitric oxide-dependent endothelial function in premenopausal women with diabetes, thereby contributing to the incidence of macrovascular complications. However, as these mechanisms do not fully explain their excess risk compared with men, other factors have been suggested, such as less aggressive risk-factor control [4,7]. Women with diabetes may be less likely to maintain HbA1c levels < 7%, to receive lipid-lowering medication, to be prescribed aspirin and, even when treated, to achieve the recommended lipid and blood pressure targets [30]. In our present study, medication use was retrieved from a 1/97 sample of patients that revealed that women with diabetes were less likely to receive ACE inhibitors, aspirin, P2Y12 inhibitors or statins than men with diabetes. Indeed, men without diabetes were more frequently treated with statins, which might also contribute to the lower HR in men. However, as these data were limited to a subset of our study population, it

must be acknowledged that this observation is only exploratory and hypothesis-generating.

Limitations

There are several limitations related to our present study. The main one is inherent, given the retrospective, observational nature of the study and its potential biases. Furthermore, the study was based on administrative data and, therefore, has limitations inherent in the methodology. The PMSI database contains diagnoses using ICD-10 codes, which are obtained at hospital discharge and are the physician's responsibility; this means that only hospitalized patients were included in our analysis. Also, the data were not systematically checked externally, and this could have created an information bias. However, the large scale of the database is likely to compensate for some of the possible biases and, as the coding of complications is linked to reimbursement and is regularly controlled, it is also likely to be of high quality.

The events included in our study were those only diagnosed while in hospital, making it impossible to analyze data for out-of-hospital deaths, although most of the major cardiovascular events analyzed in our study are never managed outside of hospital. However, because microangiopathic complications, such as proteinuria and diabetic retinopathy, usually do not require hospitalization, these complications may have been underestimated for some patients in our analysis. Moreover, such a large population of hospitalized subjects is likely to represent a highly heterogeneous group of patients admitted for various kinds of illnesses and disease severities, which may have affected the prognosis.

Another limitation is the lack of complete information in terms of therapies recommended for diabetes or cardiovascular conditions beyond the representative sample in our analysis. Of note, the EGB sample population was not extracted from the PMSI database; however, as both databases record data from the general French population, it may be speculated that the majority of patients in the EGB sample were also included in the PMSI.

Furthermore, the observational design of our analysis brings with it a risk of residual confounding factors. As our analysis was restricted to variables present in the database, this meant that some information regarding lifestyle factors (physical activity levels, diet), metabolic control (glucose levels, lipids, body mass index, blood pressure) and medical imaging (echocardiography, including measures of systolic function) were not available.

Finally, as the majority of the French population is Caucasian, our results may not be generalizable to non-Caucasian people.

Conclusion

Our present contemporary nationwide study found that, while men with diabetes have higher absolute rates of cardiovascular complications, on comparing those with and without diabetes, the RRs were higher in women than in men across all ages > 40 years. Although several putative explanations have been proposed for these findings, there are as yet no clearly defined mechanisms to explain these gender differences. However, our observations suggest that specific studies investigating more aggressive preventative measures for women with diabetes are warranted. Such measures to significantly reduce cardiovascular events in patients with T2D might include pharmacological strategies, including intensive lipid-lowering therapies, antithrombotic agents, mineralocorticoid blockade, and antidiabetic drugs such as glucagon-like peptide (GLP)-1 receptor agonists and SGLT2 inhibitors.

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Conflicts of interest

There are no conflicts of interest directly related to this article.

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The other authors have nothing to declare.

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Figure legends

Fig. 1. Incidence rates (IRs) of first-time major adverse cardiovascular events including heart failure (MACE-HF) according to: (upper) age at study inclusion by decade and stratified by diabetes status; and (lower) according to age and stratified by diabetes status and gender. PY, person-years.

Fig. 2. Overall (left) incidence rates, (centre) hazard ratios (HRs) and (right) women-to-men ratios (WMRs) for major adverse cardiovascular events (MACE) including heart failure, stratified by diabetes status (incidence rates only) and gender (incidence rates and HRs only). The HR in men is higher when WMRs are < 1; the HR in women is higher when WMRs are > 1.

Fig. 3. Hazard ratios (HRs) stratified by (upper) gender and (lower) unadjusted women-to-men ratios (WMRs) for first-time major adverse cardiovascular events including heart failure, according to age at inclusion by decade. The HR in women is higher when WMRs are > 1.

Supplementary figure legends

Fig. S1. Flow chart of patients included in the study. Major adverse cardiovascular (CV) events (MACE) include myocardial infarction, heart failure, ischaemic stroke and cardiovascular death (MACE-HF). Percentages (%) refer to the entire population with and without diabetes and, of those, the % of those experiencing MACE-HF.

Fig. S2. Incidence rates (IRs) of first-time cardiovascular events according to age by decade and gender and stratified by diabetes status: (upper) cardiovascular death; and (lower) myocardial infarction. PY, person-years.

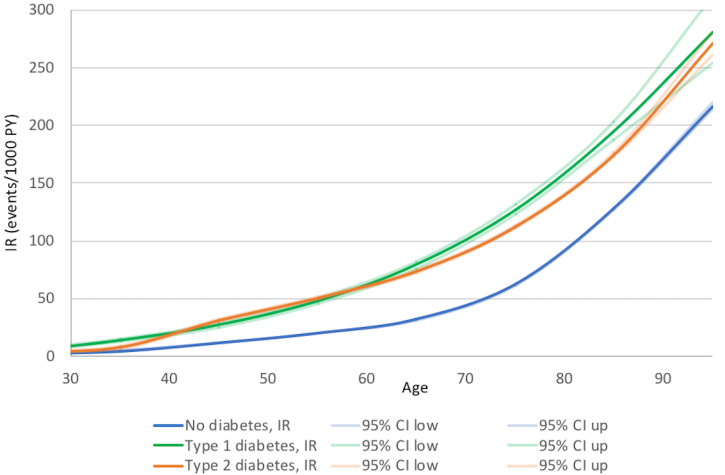
Fig. S3. Incidence rates (IRs) of first-time cardiovascular events according to age by decade and gender and stratified by diabetes status: (upper) ischaemic stroke; and (lower) heart failure. PY, person-years.

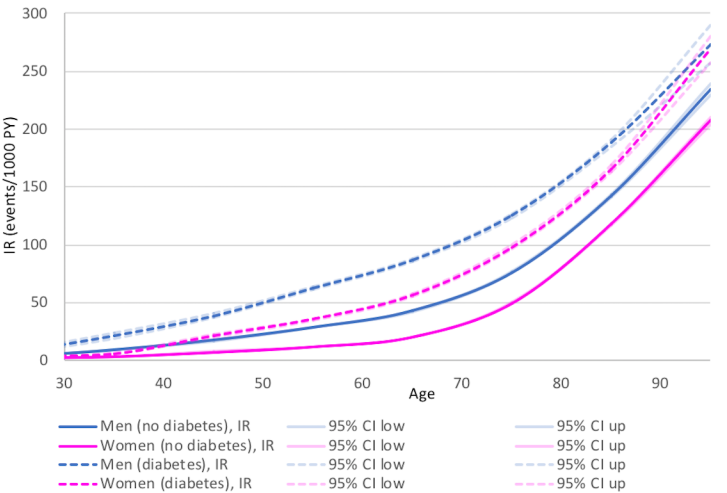
Fig. S4. Hazard ratios (HRs) stratified by (upper) gender and (lower) women-to-men ratios (WMRs) for cardiovascular death according to age by decade. The HR in women is higher when WMRs are > 1.

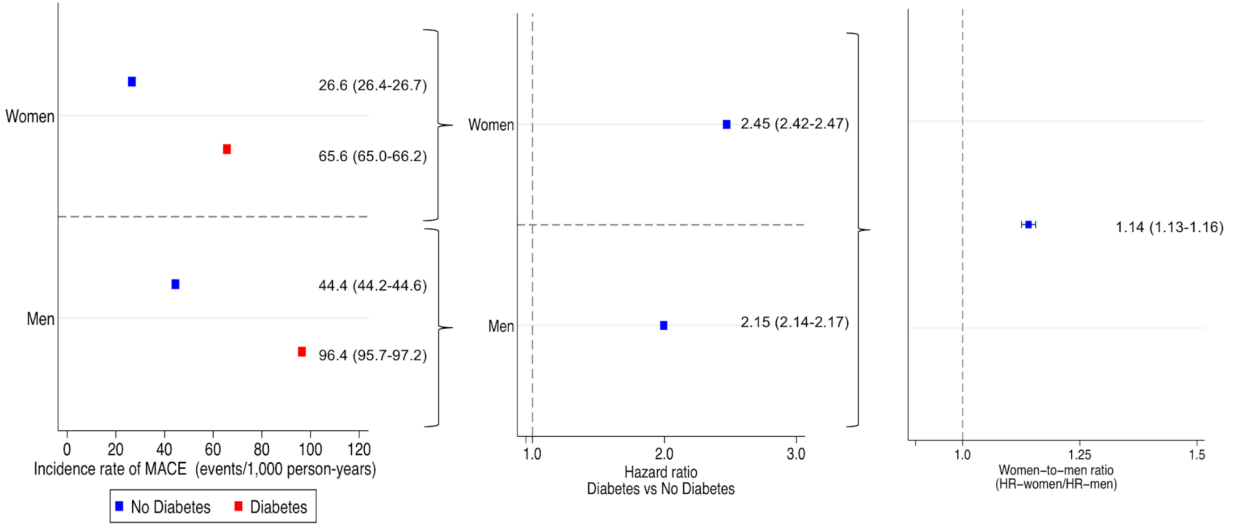
Fig. S5. Hazard ratios (HRs) stratified by (upper) diabetes status and gender, and (lower) women-to-men ratios (WMRs), for first-time myocardial infarction according to age by decade. The HR in women is higher when WMRs are > 1.

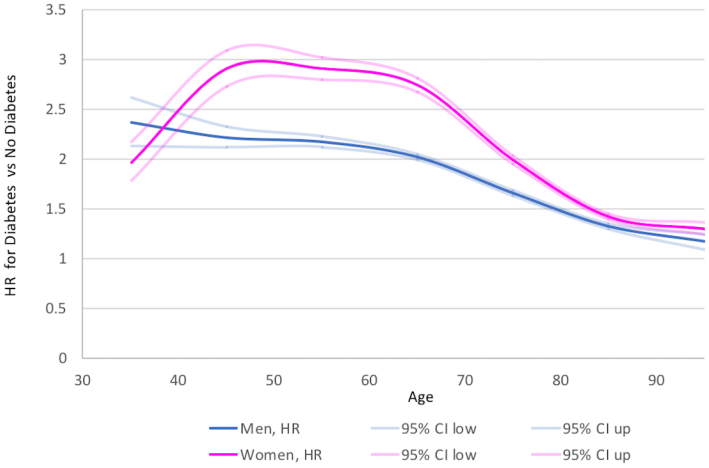
Fig. S6. Hazard ratios (HRs) stratified by (upper) diabetes status and gender, and (lower) women-to-men ratios (WMRs), for first-time ischaemic stroke according to age by decade. The HR in women is higher when WMRs are > 1.

Fig. S7. Hazard ratios (HRs) stratified by (upper) diabetes status and gender, and (lower) women-to-men ratios (WMRs), for first-time heart failure according to age by decade. The HR in women is higher when WMRs are > 1.


300
250
200
150
100
50
0
IR (events/1000 PY)
30
40
50
60
70
80
90
Age
No diabetes, IR
95% CI low
95% CI up
Type 1 diabetes, IR
95% CI low
95% CI up
Type 2 diabetes, IR
95% CI low
95% CI up


300
250
200
150
100
50
0
IR (events/1000 PY)
30
40
50
60
70
80
90
Age
Men (no diabetes), IR
95% CI low
95% CI up
Women (no diabetes), IR
95% CI low
95% CI up
Men (diabetes), IR
95% CI low
95% CI up
Women (diabetes), IR
95% CI low
95% CI up


Women
Men
26.6 (26.4-26.7)
65.6 (65.0-66.2)
44.4 (44.2-44.6)
96.4 (95.7-97.2)
0
20
40
60
80
100
120
Incidence rate of MACE (events/1,000 person-years)
No Diabetes
Diabetes
Women
Men
2.45 (2.42-2.47)
2.15 (2.14-2.17)
1.0
2.0
3.0
Hazard ratio
Diabetes vs No Diabetes
1.14 (1.13-1.16)
1.0
1.25
1.5
Women−to−men ratio
(HR−women/HR−men)


HR for Diabetes vs No Diabetes
3.5
3
2.5
2
1.5
1
0.5
0
30
40
50
60
70
80
90
Age
Men, HR
95% CI low
95% CI up
Women, HR
95% CI low
95% CI up

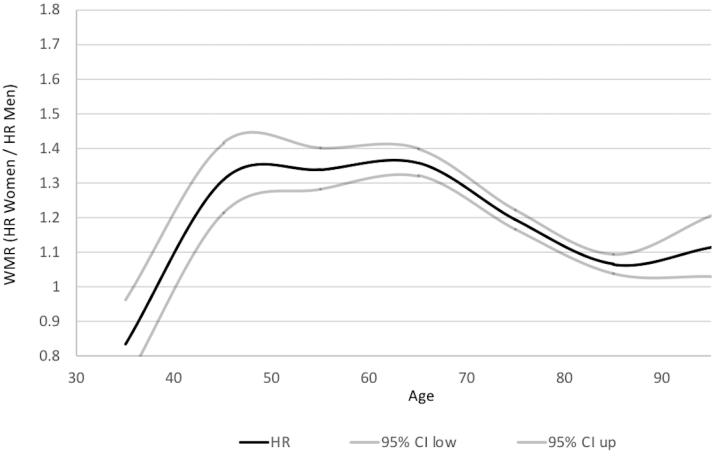

WMR (HR Women / HR Men)
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
30
40
50
60
70
80
90
Age
HR
95% CI low
95% CI up

Table I
Baseline characteristics of patients hospitalized in France in 2013 according to gender and diabetes status

	Women		**Men**	
	No diabetes (n = 1,452,669)	**Diabetes (n = 166,336)**	**No diabetes (n = 1,151,219)**	**Diabetes (n = 183,592)**
Age (years)	54.4 ± 22.2	63.1 ± 18.6	57.7 ± 21.2	66.4 ± 13.7
Hypertension	269,658 (18.6)	97,950 (58.9)	24,7678 (21.5)	117,261 (63.9)
Type 1 diabetes	0 (0.0)	21,199 (12.7)	0 (0.0)	22,678 (12.4)
Type 2 diabetes	0 (0.0)	142,702 (85.8)	0 (0.0)	157,819 (86.0)
Valve disease	19,788 (1.4)	4466 (2.7)	18,561 (1.6)	5405 (2.9)
Aortic stenosis	6704 (0.5)	2014 (1.2)	7877 (0.7)	2880 (1.6)
Aortic regurgitation	3784 (0.3)	806 (0.5)	4007 (0.3)	932 (0.5)
Mitral regurgitation	7500 (0.5)	1453 (0.9)	5757 (0.5)	1511 (0.8)
Previous endocarditis	400 (0.0)	102 (0.1)	888 (0.1)	297 (0.2)
Dilated cardiomyopathy	867 (0.1)	124 (0.1)	0 (0.0)	0 (0.0)
Coronary artery disease	30,851 (2.1)	13,119 (7.9)	67,841 (5.9)	31,509 (17.2)
Previous PCI	4444 (0.3)	2043 (1.2)	15,647 (1.4)	7048 (3.8)
Previous CABG	343 (0.0)	178 (0.1)	1595 (0.1)	865 (0.5)
Vascular disease	29,767 (2.0)	13,012 (7.8)	65,780 (5.7)	31,602 (17.2)
Atrial fibrillation	53,342 (3.7)	12,649 (7.6)	67,513 (5.9)	19,615 (10.7)
Sinus node disease	4592 (0.3)	1022 (0.6)	5414 (0.5)	1457 (0.8)
Previous pacemaker or ICD	13,911 (1.0)	3218 (1.9)	21,259 (1.8)	6397 (3.5)
Intracranial bleeding	9617 (0.7)	1444 (0.9)	11,866 (1.0)	2390 (1.3)
Smoker	62,494 (4.3)	9263 (5.6)	86,719 (7.5)	21,369 (11.6)
Dyslipidaemia	91,836 (6.3)	46,487 (27.9)	103,182 (9.0)	62,441 (34.0)
Obesity	109,487 (7.5)	54,100 (32.5)	63,099 (5.5)	46,152 (25.1)
Alcohol-related diagnoses	36,076 (2.5)	5774 (3.5)	92,214 (8.0)	20,624 (11.2)
Chronic kidney disease	19,069 (1.3)	9389 (5.6)	22,975 (2.0)	12,505 (6.8)
Diabetic retinopathy	0 (0.0)	10,577 (6.4)	0 (0.0)	11,927 (6.5)
Lung disease	84,989 (5.9)	18,135 (10.9)	102,906 (8.9)	26,389 (14.4)
Sleep apnoea syndrome	25,518 (1.8)	12,051 (7.2)	41,809 (3.6)	18,859 (10.3)
COPD	32,744 (2.3)	7515 (4.5)	61,056 (5.3)	17,277 (9.4)
Liver disease	24,377 (1.7)	10,381 (6.2)	39,508 (3.4)	16,797 (9.1)
Gastroesophageal reflux	50,099 (3.4)	5488 (3.3)	38,964 (3.4)	4905 (2.7)
Thyroid disease	85,367 (5.9)	24,243 (14.6)	19,462 (1.7)	7839 (4.3)
Inflammatory disease	71,307 (4.9)	10,234 (6.2)	52,994 (4.6)	9960 (5.4)
Anaemia	86,981 (6.0)	20,791 (12.5)	67,144 (5.8)	20,876 (11.4)
Previous cancer	174,196 (12.0)	20,523 (12.3)	200,654 (17.4)	37,597 (20.5)
Poor nutrition	38,029 (2.6)	8280 (5.0)	33,468 (2.9)	9199 (5.0)
Cognitive impairment	36,186 (2.5)	8087 (4.9)	25,559 (2.2)	6800 (3.7)
Illicit drug use	3567 (0.2)	305 (0.2)	7825 (0.7)	680 (0.4)
In-hospital death during follow-up	262,921 (18.1)	46,115 (27.7)	309,114 (26.9)	69,354 (37.8)
In-hospital cardiovascular death	42,243 (2.9)	9518 (5.7)	42,566 (3.7)	11,949 (6.5)

Values are means ± standard deviation (SD) or n (%); mean follow-up duration: 4.9 ± 1.7 years, median: 5.5 years, interquartile range: 5.1–5.8 years;
PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease

Table II
Patients' medication rates at discharge following first hospitalization in 2013 according to gender and diabetes status

	Women		Men	
	No diabetes (n = 17,277)	**Diabetes (n = 2354)**	**No diabetes (n = 12,613)**	**Diabetes (n = 2943)**
Age (years)	54.7 ± 21.5	67.8 ± 15.3	59.8 ± 17.9	67.7 ± 12.5
ACE inhibitor or ARB	3064 (17.7)	1286 (54.6)	3317 (26.3)	1731 (58.8)
Beta-blocker	2345 (13.6)	768 (32.6)	2287 (18.1)	1087 (36.9)
Diuretic	1710 (9.9)	700 (29.7)	1341 (10.6)	836 (28.4)
K-sparing diuretic	337 (2.0)	136 (5.8)	294 (2.3)	177 (6.0)
Calcium-channel blocker	1371 (7.9)	551 (23.4)	1311 (10.4)	689 (23.4)
Antiarrhythmic agents	617 (3.6)	150 (6.4)	581 (4.6)	230 (7.8)
VKA	800 (4.6)	251 (10.7)	861 (6.8)	365 (12.4)
Direct oral anticoagulant	244 (1.4)	54 (2.3)	241 (1.9)	75 (2.5)
Aspirin	1634 (9.5)	687 (29.2)	2080 (16.5)	1121 (38.1)
P2Y12 inhibitor	390 (2.3)	200 (8.5)	780 (6.2)	474 (16.1)
Statin	1972 (11.4)	1003 (42.6)	2611 (20.7)	1464 (49.7)
Any antidiabetic drug	–	2034 (86.4)	–	2565 (87.2)
Metformin	–	836 (35.5)	–	1127 (38.3)
Insulin	–	840 (35.7)	–	925 (31.4)
Sulphonylurea	–	546 (23.2)	–	786 (26.7)
GLP-1 analogue	–	112 (4.8)	–	89 (3.0)
DPP-4 inhibitor	–	245 (10.4)	–	338 (11.5)

Data are means ± standard deviation (SD) or n (%) from the French nationwide claims database *Echantillon Généraliste des Bénéficiaires* (EGB; general sample of healthcare beneficiaries) as identified from a permanent random sample (1/97) of 35,187 patients hospitalized in France in 2013 with ≥ 5 years of follow-up;
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; K, potassium; VKA, vitamin K antagonists; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase 4

Table III
Unadjusted and multivariable-adjusted hazard ratios (HRs) of outcomes of interest, including women-to-men ratio (WMR), according to diabetes status and gender

	Total number	Patients (n) with events	Diabetes, unadjusted HR (95% CI)	Diabetes, adjusted HR (95% CI)[a]	WMR, adjusted HR
MACE-HF					
Women	1,619,005	233,471	2.45 (2.42–2.47)	1.50 (1.48–1.52)	
Men	1,334,811	295,146	2.15 (2.14–2.17)	1.39 (1.37–1.40)	1.13 (1.12–1.15)
CV death					
Women	1,619,005	51,761	1.98 (1.93–2.02)	1.36 (1.33–1.39)	
Men	1,334,811	54,515	1.81 (1.77–1.85)	1.27 (1.24–1.30)	1.07 (1.04–1.11)
MI					
Women	1,619,005	29,539	2.69 (2.62–2.77)	1.85 (1.80–1.91)	
Men	1,334,811	50,467	1.91 (1.87–1.95)	1.47 (1.43–1.50)	1.43 (1.38–1.48)
Ischaemic stroke					
Women	1,619,005	41,784	1.99 (1.94–2.04)	1.41 (1.37–1.45)	
Men	1,334,811	45,328	1.79 (1.75–1.83)	1.35 (1.32–1.39)	1.10 (1.07–1.14)
Heart failure					
Women	1,619,005	178,339	2.58 (2.55–2.61)	1.55 (1.53–1.57)	
Men	1,334,811	229,261	2.28 (2.25–2.30)	1.43 (1.42–1.45)	1.13 (1.11–1.14)

[a] Adjusted for age and baseline characteristics (smoking, obesity, hypertension, dyslipidaemia, alcohol-related diagnoses, non-cardiovascular comorbidities); WMR > 1 indicates excess risk of incident events in women with prevalent diabetes *vs* men with prevalent diabetes;
MACE-HF, major adverse cardiac events including heart failure; CV, cardiovascular; MI, myocardial infarction