Discordant Short- and Long-Term Outcomes Associated With Diabetes in Patients With Heart Failure: Importance of Age and Sex

A Population Study of 5.1 Million People in Scotland

Michael R. MacDonald, MBChB; Pardeep S. Jhund, MBChB, MSc; Mark C. Petrie, MBChB; James D. Lewsey, PhD; Nathaniel M. Hawkins, MBChB; Sai Bhagra, MBChB; Nuria Munoz, MD; Fumi Varyani, MBChB; Adam Redpath, MA, MPhil, MSc; Jim Chalmers, MBChB, MSc; Kate MacIntyre, MBChB, MPH, MD; John J.V. McMurray, MD

Background—Diabetes and heart failure frequently coexist. Our aim was to assess the association between diabetes and short- and long-term outcomes in all patients admitted to the hospital for the first time with heart failure in Scotland between 1986 and 2003.

Methods and Results—A total of 116,556 patients were studied, of whom 13% (n = 15,161) had a diagnosis of diabetes. At 30 days, diabetes was associated with a lower case fatality. By 1 year, the association between diabetes and better outcome was reversed, and diabetes was a significant independent predictor of higher case fatality. The longer term risk of death associated with diabetes was greatest in younger patients. In patients aged 65 years or younger, the hazard ratio for mortality at 5 years associated with diabetes was 1.41 (95% CI, 1.31 to 1.52) for men and 1.64 (1.50 to 1.79) for women. The risk associated with diabetes was less in patients aged 75 years or older: a hazard ratio in men 1.16 (1.10 to 1.22) and in women 1.15 (1.10 to 1.20). In the younger age group the risk associated with diabetes was significantly greater in women than in men (P = 0.005 for diabetes-sex interaction). Diabetes was also a significant independent predictor of heart failure readmission, and again the risk was greatest in younger women.

Conclusions—Although diabetes was associated with a lower case fatality at 30 days, by 1 year it was a significant independent predictor of higher case fatality. The risk associated with diabetes was greatest in young patients, and in young patients the risk was greatest in women. (Circ Heart Fail. 2008;1:234-241.)

Key Words: heart failure ■ diabetes mellitus ■ morbidity ■ mortality

Diabetes and heart failure (HF) are conditions that are individually associated with high rates of premature morbidity and mortality. As both conditions are common, they frequently coexist and it is important to understand the medical consequences of this for individual patients and healthcare systems. Most of what is known about the impact of diabetes in patients with HF comes from clinical trial populations or small cohort studies and there is much less information about this relationship in “real world” patient cohorts.1–6 Every time a patient is discharged from hospital (either dead or alive) in Scotland, the event is logged in the Scottish Morbidity Record Database and then linked to all subsequent hospitalizations and death. Our aim was to assess the association of diabetes with short- and long-term outcomes in all patients hospitalized for the first time with HF in Scotland between 1986 and 2003. We focused on the relationship between diabetes and outcomes according to age and sex.

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Methods

Data Sources

Using previously described methods7 we carried out a retrospective cohort study using the record-linked Scottish Morbidity Record Database. Everyone living in Scotland (which has a population of 5.1 million) is entitled to free health care through the National Health Service; private health care accounts for a tiny proportion of overall health care activity and almost all hospital admissions are to National Health Service hospitals. Data from all National Health Service hospitals are logged in the Morbidity Record Database and the data are linked to other relevant data such as death records and hospital readmissions.
hospital discharges (alive or dead) in Scotland are collected (in the form of the Scottish Morbidity Record) and collated by the Information and Statistics Division of the National Health Service. This database is linked to the Registrar General’s death certificate data, which contains information on deaths occurring in and out of hospital. Diagnosis at discharge is coded using the international classification of diseases (ICD) system; ICD9 codes until April 1996 and ICD10 thereafter. Each patient is given a principal diagnosis and up to 5 secondary diagnoses.

Inclusion Criteria
We included all “first” (incident) hospitalizations with a “principal” (coded in the first position) discharge diagnosis of HF (ICD9 425.4, 425.5, 425.9, 428.0, 428.1, 428.9, 402, ICD10 I50, 142.0, 142.6, 142.7, 142.9) in Scotland between 1986 and 2003. A “first” discharge was defined as one with a diagnosis of HF in a primary diagnostic position, with no previous hospitalization for HF (in any diagnostic position) since 1981 i.e., a minimum of 5 years previously. The accuracy of cardiovascular diagnoses is over 91%. Patients were defined as diabetic if they had “diabetes” (ICD-9: 250; ICD-10: E10-E14) as a concomitant diagnosis at the index admission or a principal or concomitant diagnosis within the 5 years before the index admission. Diabetes is correctly recorded as a comorbidity in 72% of discharges where the primary diagnosis is a cardiovascular cause (personal communication, ISD Data Quality, ISD Edinburgh, UK).

Data
Data were available on each patient’s age, sex, postcode of residence, date of discharge, previous and subsequent discharges, and date of death if it occurred. Comorbidity was defined as any concomitant diagnosis coded during the index admission or a principal or concomitant diagnosis within the 5 years before the index admission. Each comorbidity was identified with the following ICD codes: arthritis (ICD-9: 710 to 719; ICD-10: M00 to M25); atrial fibrillation (ICD-9: 427.3; ICD-10: I48); cancer (ICD-9: 140 to 208; ICD-10: C00 to C99); cerebrovascular disease (ICD-9:430 to 438; ICD-10: I60 to I69, G45); acute myocardial infarction (ICD-9: 410; ICD-10: I10, I21, I22); coronary heart disease (ICD-9: 411 to 414; ICD-10: I20, I23, I24, I25); hypertension (ICD-9: 40; ICD-10: I10 to I13); peripheral arterial disease (ICD-9: 440 to 448; ICD-10: I70 to I78); renal failure (ICD-9: 584 to 586; ICD-10: N17 to N19); respiratory disease (ICD-9: 480 to 496; ICD-10: J10 to J18, J40 to J47). We used postcode sectors to allocate Carstairs deprivation quintiles on the basis of 4 variables from the 1991 census, namely male unemployment, overcrowding, social class, and car ownership.

Statistical Analysis
The prevalence of diabetes in each year of admission was calculated and rates were directly standardized to the age and sex distribution of the patients in Scotland hospitalized with HF for the first time in 2001.

Kaplan-Meier analyses were used to determine median survival times. Crude case fatality and readmission rates were calculated from the date of HF diagnosis to 30 days and from 30 days to 1 year and 30 days to 5 years using the actuarial life-table method. This method takes account of hospitalization dates and periods of follow-up which differ between patients. Patients were divided into 1 of 3 age-group categories: <65 years, 65 to 74 years, and >74 years of age. Rates for men and women with and without diabetes were calculated separately.

Outcomes at 30 days were analyzed using a logistic regression model which included history of diabetes, age, socioeconomic deprivation, year of admission, and comorbidity (myocardial infarction, atrial fibrillation, arthritis, cancer, cerebrovascular disease, coronary heart disease, renal failure, hypertension, peripheral vascular disease, respiratory disease). Cox proportional hazards analysis was used to examine the independent effect of diabetes on outcomes in patients surviving for >30 days. The models included diabetes, comorbidities, year of admission, deprivation index and age. Interaction terms were included in the full multivariate model to examine the relationship between diabetes and sex and diabetes and age. A deviance test was then performed to assess the impact of the interaction terms on the fit of the models. The probability values for the deviance tests are quoted in the tables to describe the strength of the interaction. When a significant interaction was detected, the effect of diabetes was examined in separate models according to age (<65, 65 to 74, and >74) and sex. Patients not assigned a deprivation score were excluded from these analyses.

Significance was accepted at the 0.05 level. All analyses were undertaken using the statistical package for social scientists (SPSS Inc., Chicago, Ill). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Baseline Characteristics and Prevalence of Diabetes
Table 1 describes the baseline characteristics of 116,556 individuals discharged from hospital between 1986 and 2003 with a diagnosis of HF according to history of diabetes and sex. Fifteen thousands one hundred sixty-one individuals (7356 [13.3%] men, 7805 [12.7%] women) had a history of diabetes. The reported prevalence of diabetes increased over the duration of the study in both men (from 7.3% to 19.5%) and women (from 9.1% to 19.0%) (Figure 1). Diabetics were younger (P<0.001), with a median age of 71 years for men and 75 years for women, in comparison with 73 and 79 years for nondiabetic men and women, respectively. Diabetics were more likely to have coronary heart disease, peripheral arterial disease, cerebrovascular disease, hypertension, and renal failure. The distribution of patients according to deprivation status was similar in those with and without diabetes.

Median Survival
After a first admission to hospital with HF, the median survival time in men with diabetes was 572 days (interquartile range: 92 to 1736) and in men without diabetes was 620 days (interquartile range: 68 to 2090). Median survival time in women was lower than in men; 507 days (interquartile range: 85 to 1511) for diabetics and 538 days (interquartile range: 52 to 1854) for nondiabetics.

Case Fatality
Unadjusted
Patients with diabetes had lower case fatality rates at 30 days than those without diabetes. The 30-day case fatality rate in women was 16.3% in diabetics and 20.4% in nondiabetics (P<0.0001) and in men was 16.0% and 18.8% for diabetics and nondiabetics, respectively (P<0.0001) (Table 2, Figure 2). Longer term case fatality was higher in diabetics: at 5 years it was 71.4% in diabetic men and 65.4% in nondiabetic men (P<0.0001). In women these figure were 75.5% and 68.0% for diabetics and nondiabetics, respectively (P<0.0001) (Table 2 and Figure 3). In both men and women, diabetes was particularly associated with a higher case fatality in younger age groups (Figure 3).

Adjusted
After adjustment for age, comorbidity, deprivation, and year of admission, diabetes was a significant independent predic-
tor of a lower case-fatality rate at 30 days. In contrast, at 1-year, diabetes was a significant independent predictor of higher case fatality (Table 3).

Case Fatality at 1 Year
At 1 year, the risk associated with diabetes was similar in men of all ages. However, in women the risk was greatest in patients <65 years of age, with a hazard ratio of 1.43 (95% CI, 1.25 to 1.64), declining to a hazard ratio of 1.09 (1.02 to 1.15) in patients ≥74 years of age (age-diabetes interaction P<0.001).

Case Fatality at 5 Years
Diabetes was an independent predictor of higher 5-year case fatality, regardless of age category (Table 3 and Figure 4). However, the risk associated with diabetes was greater in the younger than older age groups for both men and women, with a statistically significant interaction between diabetes and age in both men (P<0.001) and women (P<0.001). In the younger age groups, women had an even greater risk associated with diabetes than men. There were highly significant interactions between diabetes and sex for patients <65 years of age (P=0.005) and for those between 65 and 74 years of age (P<0.0001), but not for patients older than 74 years of age (P=0.523).

HF Readmission
At 30 days, 1 year, and 5 years diabetics generally had higher unadjusted rates of readmission with HF than nondiabetics (Table 2). At 30 days, in contrast to case fatality, diabetes was a significant independent predictor of HF readmission in both men and women. The risks of HF readmission at 1 and 5

Table 1. Baseline Characteristics of Patients Admitted With a First Hospitalization for HF

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>No Diabetes</th>
<th>Diabetes</th>
<th>No Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>3806 (8.0%)</td>
<td>7507 (14.0%)</td>
<td>663 (9.0%)</td>
<td>1037 (13.3%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9466 (19.8%)</td>
<td>10 526 (19.7)</td>
<td>1424 (19.4%)</td>
<td>1572 (20.1%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>4088 (8.6%)</td>
<td>3548 (6.6%)</td>
<td>550 (7.5%)</td>
<td>502 (6.4%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4639 (9.7%)</td>
<td>4937 (9.2%)</td>
<td>1043 (14.2%)</td>
<td>1096 (14.0%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9354 (19.6%)</td>
<td>8154 (15.2%)</td>
<td>1786 (24.3%)</td>
<td>1691 (21.7%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>18 131 (37.9%)</td>
<td>16 891 (31.5%)</td>
<td>3879 (52.7%)</td>
<td>3825 (46.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5309 (11.1%)</td>
<td>6689 (12.5%)</td>
<td>1893 (25.7%)</td>
<td>2059 (26.4%)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4448 (9.3%)</td>
<td>3483 (6.5%)</td>
<td>1407 (19.1%)</td>
<td>1062 (13.6%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3958 (8.3%)</td>
<td>4070 (7.6%)</td>
<td>1020 (13.9%)</td>
<td>1054 (13.5%)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>10 298 (21.5%)</td>
<td>9827 (18.3%)</td>
<td>1564 (21.3%)</td>
<td>1550 (19.9%)</td>
</tr>
<tr>
<td>Deprivation category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (least deprived)</td>
<td>7267 (15.2%)</td>
<td>7782 (14.5%)</td>
<td>1023 (13.9%)</td>
<td>940 (12.0%)</td>
</tr>
<tr>
<td>II</td>
<td>8828 (18.5%)</td>
<td>9700 (18.1%)</td>
<td>1379 (18.8%)</td>
<td>1249 (16.0%)</td>
</tr>
<tr>
<td>III</td>
<td>9319 (19.5%)</td>
<td>7782 (19.1%)</td>
<td>1495 (20.3%)</td>
<td>1479 (19.0%)</td>
</tr>
<tr>
<td>IV</td>
<td>9522 (19.9%)</td>
<td>10 697 (20.0%)</td>
<td>1577 (21.4%)</td>
<td>1779 (22.8%)</td>
</tr>
<tr>
<td>V (most deprived)</td>
<td>11 566 (24.2%)</td>
<td>13 825 (25.8%)</td>
<td>1737 (23.6%)</td>
<td>2208 (28.3%)</td>
</tr>
</tbody>
</table>

HF indicates heart failure.
years are shown in Table 3. In men, at 1 and 5 years diabetes was a significant independent predictor of HF readmission with a risk that remained constant across all age groups. However, in women at 1 year there was a trend toward a greater risk associated with diabetes in the younger patients than in the older patients. By 5 years this was statistically significant (diabetes-age interaction, \( P < 0.001 \)). This greater risk in young women, in comparison with men, is emphasized by the presence of a significant interaction between diabetes and sex in patients \(<75\) years of age.

**Death or HF Readmission**

For the combined end point of death or HF readmission, a similar pattern of risk was seen as with case fatality (Tables 2 and 3). At 30 days, diabetes was associated with an apparently lower risk in both men and women. At 1 year, the risk in men was constant across all age categories, but at 5 years there was a significantly greater risk in the younger age groups. In women \(<65\) years of age, at both 1 and 5 years there was a significantly greater risk associated with diabetes than in men \(<65\) years and women \(>74\) years of age.

**Discussion**

This analysis from the Scottish Morbidity Records Database is the largest study to date to examine the relationship between diabetes and clinical outcomes in a contemporary “real life” population with HF. No other study has examined data on individuals with HF and coexisting diabetes from a whole country over such a long time period. We describe several key findings. Surprisingly, diabetes was an independent predictor of lower case fatality at 30 days. By 1 year, the association between diabetes and better outcome had reversed and diabetes was a significant independent predictor of higher case fatality. The risk of death associated with diabetes was greatest in younger patients and, in particular, younger women. Diabetes was also a significant independent predictor of HF readmission, and again the risk was greatest in younger women.

**Reported Prevalence of Diabetes**

The reported prevalence of diabetes in patients with HF is highly variable, likely due to both the definitions of diabetes and HF used and the heterogeneous nature of the populations studied.\(^9\)–\(^11\) The overall prevalence of diabetes in our population (13%) was similar to the prevalence of diabetes in patients hospitalized with HF in the Danish Investigations of Arrhythmia and Mortality on Dofetilide–HF study (16%).\(^4\)

Given the diagnostic accuracy of diabetes in our study, it is likely that the true prevalence of diabetes is marginally higher
than this. The change in the prevalence of diabetes over time is in-keeping with results from a population of patients from Olmsted county, Minnesota with incident HF.3 In Olmsted, the prevalence of diabetes increased from 13% in 1979 to 1984% to 25% between 1995 and 1999. It is likely that the increasing prevalence of diabetes is related to changing definitions, increased disease recognition and the increasing prevalence of obesity.

**Table 2. Continued**

<table>
<thead>
<tr>
<th></th>
<th>HF Readmission</th>
<th></th>
<th>Death or HF Readmission</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>Nondiabetic</td>
<td>Diabetic</td>
<td>Nondiabetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic</td>
<td>Nondiabetic</td>
</tr>
<tr>
<td>8.4 (7.7–9.1)</td>
<td>6.8 (6.5–7.0)</td>
<td>7.1 (6.5–7.7)</td>
<td>5.2 (5.0–5.4)</td>
<td>22.8 (21.8–23.8)</td>
</tr>
<tr>
<td>9.2 (7.9–10.5)</td>
<td>8.0 (7.5–8.6)</td>
<td>8.4 (6.9–7.9)</td>
<td>6.9 (6.3–7.6)</td>
<td>18.3 (16.6–20.0)</td>
</tr>
<tr>
<td>8.8 (7.6–9.9)</td>
<td>7.1 (6.6–7.5)</td>
<td>7.1 (6.1–8.2)</td>
<td>5.9 (5.4–6.3)</td>
<td>22.1 (20.6–23.7)</td>
</tr>
<tr>
<td>7.3 (6.2–8.4)</td>
<td>5.8 (5.5–6.2)</td>
<td>6.6 (5.7–7.4)</td>
<td>4.6 (4.4–4.9)</td>
<td>27.1 (25.4–28.9)</td>
</tr>
<tr>
<td>38.9 (37.5–40.2)</td>
<td>31.2 (30.7–31.7)</td>
<td>38.0 (36.7–39.3)</td>
<td>29.1 (28.6–29.6)</td>
<td>50.7 (49.4–52.0)</td>
</tr>
<tr>
<td>36.1 (33.7–38.5)</td>
<td>30.2 (29.3–31.2)</td>
<td>36.6 (33.7–39.6)</td>
<td>25.7 (24.4–27.0)</td>
<td>44.4 (42.0–46.8)</td>
</tr>
<tr>
<td>39.1 (36.9–41.3)</td>
<td>30.0 (29.1–30.9)</td>
<td>39.3 (37.0–41.6)</td>
<td>28.8 (27.8–29.8)</td>
<td>50.2 (48.1–52.3)</td>
</tr>
<tr>
<td>41.5 (39.0–44.0)</td>
<td>32.7 (31.9–33.5)</td>
<td>37.7 (35.8–39.6)</td>
<td>29.9 (29.3–30.5)</td>
<td>57.0 (54.8–59.3)</td>
</tr>
<tr>
<td>70.2 (68.7–71.7)</td>
<td>58.8 (58.2–59.4)</td>
<td>69.8 (68.3–71.3)</td>
<td>57.6 (57.0–58.2)</td>
<td>85.0 (84.0–86.0)</td>
</tr>
<tr>
<td>66.1 (63.5–68.7)</td>
<td>52.8 (51.7–54.0)</td>
<td>63.6 (60.3–66.8)</td>
<td>47.2 (45.7–48.8)</td>
<td>78.5 (76.5–80.5)</td>
</tr>
<tr>
<td>69.4 (66.9–71.9)</td>
<td>57.7 (56.6–58.8)</td>
<td>71.5 (69.0–74.0)</td>
<td>55.5 (54.3–56.7)</td>
<td>84.7 (83.1–86.4)</td>
</tr>
<tr>
<td>76.3 (73.5–79.0)</td>
<td>64.9 (63.9–65.9)</td>
<td>71.9 (69.6–74.3)</td>
<td>61.4 (60.6–62.2)</td>
<td>91.3 (89.9–92.7)</td>
</tr>
</tbody>
</table>

**Short-Term Outcomes**

In Scotland, among patients hospitalized for the first time with HF, diabetics had a lower 30-day case fatality rate than nondiabetics. This association was seen across all age groups in both men and women and even after adjustment for comorbidity, age, deprivation, and year of admission. Why might diabetes be associated with better short-term survival after a first hospitalization for HF? It has previously been shown that in patients with HF, diabetes is associated with more severe symptoms for a given ejection fraction.12,13 It has also been noted that following myocardial infarction, diabetics have a higher incidence of HF, despite less of a reduction in left ventricular systolic function.14 In our analysis, we have been unable to adjust for ejection fraction. However, it is possible that diabetics in our population had higher ejection fractions than the nondiabetics and accordingly, better short-term survival. The findings of the only other study to compare the short-term prognosis of patients hospitalized with HF with and without diabetes (but which did not report long-term outcomes) are consistent with this hypothesis. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry, which enrolled 5791 patients hospitalized with HF in the United States,15 diabetes was associated with a lower 60- to 90-day mortality (6.2% versus 9.2%, P=0.008) in patients with preserved left ventricular systolic function whereas in patients with reduced left ventricular systolic function the 60- to 90-day mortality rates were not significantly different in diabetics and nondiabetics (9.4% versus 7.6%, P=NS).

In contrast to case fatality, our data suggest that, in the short term, diabetes is associated with a greater risk of HF readmission. However, this difference is not apparent when the combined end point of death or HF readmission is examined. It is likely that the higher rates of HF readmission seen in the short term are a result of competing risks. With fewer diabetics dying in the first 30 days, proportionally more are exposed to the risk of HF readmission than nondiabetics.

![Figure 3. Unadjusted 30-day to 5-year case fatality in male and female patients with and without diabetes among individuals surviving 30 days after discharge. Vertical bars represent 95% confidence intervals.](http://circheartfailure.ahajournals.org/doi/fig/10.1161/01.CIR.0000327125.42474.6E)
Table 3. Risk of Death, HF Readmission and Death, or HF Readmission at 1 and 5 Years Associated With Diabetes. Hazard Ratios (HR) for the Association With Diabetes Compared With No Diabetes Have Been Adjusted for Comorbidities, Year of Admission, and Socioeconomic Deprivation

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Overall</th>
<th>&lt;65</th>
<th>65–74</th>
<th>&gt;74</th>
<th>Diabetes and Age Interaction Test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males HR (±95%)</td>
<td>0.88 (0.82–0.94)</td>
<td>0.91 (0.77–1.07)</td>
<td>0.82 (0.73–0.93)</td>
<td>0.88 (0.80–0.98)</td>
<td>0.427</td>
</tr>
<tr>
<td>Females HR (±95%)</td>
<td>0.79 (0.74–0.84)</td>
<td>0.78 (0.64–0.95)</td>
<td>0.86 (0.76–0.98)</td>
<td>0.75 (0.69–0.82)</td>
<td>0.522</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.170</td>
<td>0.752</td>
<td>0.054</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.11 (1.01–1.23)</td>
<td>1.06 (0.89–1.27)</td>
<td>1.12 (0.95–1.31)</td>
<td>1.16 (0.97–1.38)</td>
<td>0.705</td>
</tr>
<tr>
<td>Females</td>
<td>1.21 (1.09–1.34)</td>
<td>1.11 (0.88–1.40)</td>
<td>1.10 (0.91–1.32)</td>
<td>1.35 (1.17–1.57)</td>
<td>0.202</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.752</td>
<td>0.752</td>
<td>1</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>Death or HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.94 (0.89–1.00)</td>
<td>0.95 (0.84–1.08)</td>
<td>0.91 (0.82–1.01)</td>
<td>0.94 (0.86–1.04)</td>
<td>0.779</td>
</tr>
<tr>
<td>Females</td>
<td>0.88 (0.83–0.93)</td>
<td>0.88 (0.75–1.04)</td>
<td>0.92 (0.83–1.03)</td>
<td>0.84 (0.78–0.91)</td>
<td>0.705</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.400</td>
<td>1</td>
<td>0.180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days to 1 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.11 (1.05–1.16)</td>
<td>1.19 (1.06–1.34)</td>
<td>1.05 (0.96–1.14)</td>
<td>1.09 (1.01–1.18)</td>
<td>0.22</td>
</tr>
<tr>
<td>Females</td>
<td>1.16 (1.11–1.22)</td>
<td>1.43 (1.25–1.64)</td>
<td>1.14 (1.04–1.25)</td>
<td>1.09 (1.02–1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.038</td>
<td>0.087</td>
<td>0.526</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.24 (1.18–1.30)</td>
<td>1.18 (1.07–1.29)</td>
<td>1.27 (1.17–1.38)</td>
<td>1.25 (1.15–1.36)</td>
<td>0.157</td>
</tr>
<tr>
<td>Females</td>
<td>1.27 (1.21–1.33)</td>
<td>1.40 (1.24–1.58)</td>
<td>1.33 (1.22–1.46)</td>
<td>1.20 (1.12–1.29)</td>
<td>0.160</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.317</td>
<td>0.465</td>
<td>0.783</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Death or HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.17 (1.12–1.22)</td>
<td>1.16 (1.07–1.26)</td>
<td>1.17 (1.09–1.25)</td>
<td>1.15 (1.07–1.23)</td>
<td>0.83</td>
</tr>
<tr>
<td>Females</td>
<td>1.19 (1.14–1.24)</td>
<td>1.38 (1.24–1.53)</td>
<td>1.24 (1.15–1.33)</td>
<td>1.10 (1.04–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.003</td>
<td>0.212</td>
<td>0.707</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>30 days to 5 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.23 (1.19–1.27)</td>
<td>1.41 (1.31–1.52)</td>
<td>1.20 (1.13–1.27)</td>
<td>1.16 (1.10–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Females</td>
<td>1.29 (1.25–1.33)</td>
<td>1.64 (1.50–1.79)</td>
<td>1.36 (1.29–1.45)</td>
<td>1.15 (1.10–1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>0.523</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.29 (1.24–1.34)</td>
<td>1.31 (1.22–1.41)</td>
<td>1.28 (1.19–1.36)</td>
<td>1.28 (1.20–1.37)</td>
<td>0.96</td>
</tr>
<tr>
<td>Females</td>
<td>1.32 (1.27–1.37)</td>
<td>1.47 (1.34–1.62)</td>
<td>1.42 (1.33–1.52)</td>
<td>1.22 (1.15–1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.023</td>
<td>0.016</td>
<td>0.418</td>
<td>…</td>
<td></td>
</tr>
<tr>
<td>Death or HF readmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.23 (1.19–1.27)</td>
<td>1.30 (1.22–1.39)</td>
<td>1.20 (1.14–1.27)</td>
<td>1.18 (1.12–1.24)</td>
<td>0.006</td>
</tr>
<tr>
<td>Females</td>
<td>1.26 (1.23–1.30)</td>
<td>1.50 (1.39–1.63)</td>
<td>1.35 (1.28–1.43)</td>
<td>1.14 (1.09–1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes and sex interaction test (P)</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.639</td>
<td>…</td>
<td></td>
</tr>
</tbody>
</table>

HF indicates heart failure.
Long-Term Outcomes
If the above hypothesis is correct, what is striking and intriguing is the reversal, in the longer term, of the short-term “protective” association between diabetes and mortality. The implication is that the adverse effects of diabetes are so powerful that within a year of discharge they have overcome any survival advantage related to a higher ejection fraction. Our findings are consistent with a recent report from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity program, which showed that diabetes has a greater impact on mortality and morbidity in patients with higher ejection fractions.

Long-Term Outcomes: the Interaction Between Diabetes and Age
There was a significant interaction between diabetes and age in both men and women. The risk associated with diabetes declined with advancing age. This has not been previously described and may be partly explained by competing risks. Because of the extremely high 5-year risk of death in very elderly patients, it is unlikely that diabetes could have significantly increased that risk.

Long-Term Outcomes: the Interaction Between Diabetes and Sex
At 5 years, diabetes was also associated with a greater risk of death in women than in men. This divergence in risk diminished with advancing age. Our finding is consistent with prior analyses of the Danish Investigations of Arrhythmia and Mortality on Dofetilide–HF and the Digitalis Investigation Group trials, which also identified an interaction between diabetes and sex in patients with HF. In Danish Investigations of Arrhythmia and Mortality on Dofetilide–HF, diabetes (present in 900 of 5491 patients randomized) was associated with a greater risk of death in women than in men, with relative risks of 1.7 (1.4 to 1.9) and 1.4 (1.3 to 1.6) for women and men, respectively. In patients in the Digitalis Investigation Group trial aged <65 years of age, the risk associated with diabetes (compared with no diabetes) was 1.69 (1.16 to 2.50) for women and 1.21 (1.01 to 1.45) for men (test for interaction, \(P=0.173\)). For patients \(\geq 65\) years, the risk associated with diabetes for women was 1.87 (1.43 to 2.46) and in men 1.20 (1.03 to 1.40) (interaction, \(P=0.005\)).

We extended these prior observations to show that this difference in risk between men and women is also seen for HF hospitalization as well as death.

Why is the risk associated with diabetes greater in women than in men? This interaction seems to be present in other forms of cardiovascular disease and the explanation for this may be multifactorial in origin. There may be a biological explanation for this difference. Diabetes may modify the cardiovascular risk profiles of women in a more detrimental way. There also may be treatment differences. Coronary heart disease risk factors may not be treated as intensively in diabetic women as they are in diabetic men. Also, it is possible that women present to hospital with more advanced HF than men and may have more extensive coronary disease. Furthermore, women with acute HF are more likely to have a preserved ejection fraction than men and as mentioned above, the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity investigators have reported that diabetes has a greater impact on mortality and morbidity in patients with higher ejection fractions.

Limitations
The major limitation of this study relates to the nature of the large routine administrative database which we analyzed. Although it has the strength of identifying all outcome data for a whole country, it has the weakness of collecting a relatively restricted set of baseline data. Important confounders such as left ventricular ejection fraction, the duration and severity of diabetes, body mass index, and drug and device therapy were not collected. Another limitation is that the diagnosis of HF, diabetes, and comorbidities was made retrospectively, using routine discharge coding rather than by prospective detailed evaluation of patients. This is evident in the diagnostic accuracy of diabetes, which we measured as 72%. We feel this figure is reasonably high for databases of this type, and if anything will likely lead to an underestimation of the effect associated with diabetes.

Conclusion
This is the largest study to date examining the risk associated with diabetes in patients hospitalized with HF. The lower case fatality in diabetics at 30 days is a short-term feature and by 1 year diabetes is an independent predictor of higher case fatality. The risk associated with diabetes is greatest in young patients. In these young patients, the risk is greatest in women. Further work is needed to examine why women are at greater risk from diabetes than men. Prospective studies in well-characterized populations may help delineate the biological differences that lead to the divergence in risk between men and women. Given that the greatest risk appears to be in the youngest patients, this age group stands to gain the most from timely intervention and further research into the treatment of diabetes in patients with HF is warranted. Furthermore, substantial benefit may be gained from investigation into the prevention of diabetes in patients with HF.

Disclosures
None.
References


CLINICAL PERSPECTIVE

In patients hospitalized with heart failure, diabetes mellitus was associated with better short-term outcomes, but by 1 year after discharge, this effect was reversed, with diabetics experiencing higher mortality and morbidity. The risk related to diabetes was greater in younger than older patients and women compared with men. The explanation for this change in risk over time is unknown.
Discordant Short- and Long-Term Outcomes Associated With Diabetes in Patients With Heart Failure: Importance of Age and Sex: A Population Study of 5.1 Million People in Scotland

Michael R. MacDonald, Pardeep S. Jhund, Mark C. Petrie, James D. Lewsey, Nathaniel M. Hawkins, Sai Bhagra, Nuria Munoz, Fumi Varyani, Adam Redpath, Jim Chalmers, Kate MacIntyre and John J.V. McMurray

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