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Original Article

Sex differences in cardiovascular outcomes, pharmacological treatments and indicators of care in patients with newly diagnosed diabetes: Analyses on administrative database

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ABSTRACT

Background: The impact of diabetes on cardiovascular disease in both sexes is known, but the specifics have not been fully clarified. We investigated whether sex-related differences exist in terms of management and hospitalization in patients with newly diagnosed diabetes.

Methods: We examined the rates of hospitalization for cardiovascular causes, mortality, treatments and management of patients with diabetes compared to subjects without, from administrative database. Interaction between sex and diabetes on clinical outcomes were calculated using a Cox regression model. Pharmacological treatments and recommended examinations by sex were calculated using logistic regression.

Results: From 2002 to 2006, 158,426 patients with diabetes and 314,115 subjects without were identified and followed up for a mean of 33 months (±17.5).

Diabetes confers a higher risk for all clinical outcomes. Females with diabetes have a risk profile for hospitalization for coronary heart disease comparable to males without (4.6% and 5.3%). Interaction between sex and diabetes shows that females with diabetes had an added 19% higher risk of total death (95% CI 1.13–1.24). No differences were observed in hospitalizations, although females with diabetes were less likely to undergo revascularization after myocardial infarction. Females received cardiovascular prevention drugs less frequently than males and had a slight tendency to get fewer examinations.

Conclusion: Diabetes is linked to a higher increase of mortality in females relative to males. This might reflect sex differences in the use of revascularization procedures or therapeutic regimens. Closer attention and implementation of standard care for females are necessary from the onset of diabetes.

1. Introduction

Diabetes is one of the main health problems worldwide as a consequence of the progressive aging of the population, the spread of obesity and unhealthy lifestyles [1–3]. Sex differences in the impact of diabetes on the development and/or progression of cardiovascular disease have already been highlighted [4–7]. Females with diabetes have four times higher risk of total mortality compared with those without whereas the risk of coronary mortality was more than double compared to males with diabetes [8,9], though all-cause mortality among subjects with diabetes has declined over time irrespective of sex [10–12]. These disparities may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with a reduced likelihood of women receiving standard treatment compared to men [4]. However, sex differences regarding the risk of coronary heart disease mortality were canceled after adjusting for major cardiovascular risks [13]. Patients' greater awareness about the control of cardiovascular risk factors and physicians' attitude to be more aggressive in their management could have reduced the sex-related differences observed previously [14,15].

This study investigated whether there are sex-related differences in a cohort of subjects with newly diagnosed diabetes, identified from a

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regional administrative database, in cardiovascular outcomes, prescription of pharmacological treatments, and decisions about laboratory or diagnostic investigations.

2. Methods

2.1. Data sources and inclusion criteria

We used linkable administrative health databases of the Lombardy Region. Data were available from 2000 to 2007. Lombardy is the most densely populated Italian region, with a population of more than 9 million in 2007. It comprises urban, industrialized and rural areas. In Italy, the health care system (NHS) is government-run; all residents have a personal identification number recorded in the National Civil Registration System (NCRS).

The regional database contains demographic data on all residents. The pharmacy prescription database contains information on medication name and relative anatomic therapeutic chemical (ATC) classification code, quantity and dispensation date. The hospital discharge database (HDD) records information on date of hospital admission, date of discharge or death, diagnosis, and procedures performed. Laboratory tests and specialist medical examinations are also recorded.

All these databases are linked anonymously with the demographic data using unique encrypted patient codes in accordance with Italian laws for the treatment of confidential data.

All persons with diabetes can obtain anti-diabetic drugs, laboratory tests, visits and diabetes devices free of charge from the NHS, provided they have a certificate of diabetes diagnosed by a physician working in a public health institution. This certificate is recorded in a specific database called the disease-specific exemption registry (ER). Type 1 and type 2 diabetes cannot be classified separately from the information in the ER so the type of diabetes is not considered in this paper.

To be included in the study, patients had to fulfill one of the following criteria:

- Prescription of an oral anti-diabetic drug (OAD) or insulin according to ATC-code A10*. To reduce the risk of including false-positive subjects we considered as patients with diabetes who received at least 30% of the defined daily dosages (DDD) of each anti-diabetic drug;
- Diagnosis-related group (DRG) hospitalization code for diabetes (DRG codes 294 and 295) entered in the HDD;
- Diabetes diagnosis certification (013.250) entered in the ER.

2.2. Study cohort

All persons aged 40–89 years, who met at least one of the above criteria between 2002 and 2006, but had not been diagnosed with diabetes in the previous two years, were considered as newly diagnosed type 2 diabetes patients. Although information on diabetes type was not available, the patients' ages suggest that most had type 2-diabetes. The comparison cohort consisted of two subjects without diabetes for each case, matched for age (± 1 year), sex and general practitioner referral. All participants were followed up until the first hospitalization for cardiovascular reason, death, emigration or admission to a nursing home, or until December 31, 2007.

2.3. Cardiovascular events, surgical procedures and death

We recorded the first-ever event in patients with diabetes and control cohort as hospital admission for coronary heart disease (CHD), myocardial infarction (MI), heart failure (HF), cerebrovascular disease (CVD), stroke and death, starting from the year after entering the cohort. Codes (reported in the appendix) for the primary diagnosis and coronary revascularization procedures were used according the ICD-9-CM classification.

2.4. Pharmacological treatments

From 2002 to 2006, anti-diabetic and cardiovascular drug prescriptions were recorded for patients with diabetes, according to sex. All drugs were classified according to the ATC code. The following classes of anti-diabetic drugs were considered: sulfonylureas (A10BB), biguanides (A10BA), glinides (A10BX), glitazones (A10BG) and insulin (A10A). Acarbose (A10BF) was not included in our analysis since this drug is not covered by the NHS. The following cardiovascular classes were considered: angiotensin converting enzyme inhibitors (ACE-inhibitors) or angiotensin receptor blockers (ARBs) (C09), lipid-lowering drugs (C10) and antiplatelet drugs (B01AC).

2.5. Laboratory tests and special medical exams

Laboratory tests and special medical exams were recorded from 2002 to 2006, and at least one of the following investigations per year was considered an indicator of healthcare quality: glycated hemoglobin (HbA1c), fasting blood glucose, serum cholesterol (total, HDL, LDL), triglycerides, creatinine, microalbuminuria, cardiovascular examinations (including ECG), and ophthalmological visit (including fundus oculi, electroretinography and fluorescein-angiography).

2.6. Statistical analysis

Patients were grouped in ten year brackets (40–49, 50–59, 60–69, 70–79 and 80–89 years) taking as reference the most numerous decade: 60–69 years. Males were the reference group for sex. Concomitant medications were grouped in classes with similar frequencies. The reference group for medication use was the group that took fewer than two concomitant drugs (as a proxy for the healthiest subjects). Subjects were considered censored upon death (except for analyses in which death was the outcome), emigration and admission to a nursing home.

Characteristics of males and females with diabetes were compared using univariate analysis with the Chi-squared test. Incidences of events were plotted using Kaplan–Meier survival curves comparing patients with diabetes and subjects without diabetes, males and females.

The hazard ratios (HR) of the interaction between sex and diabetes for first hospital admission and for total mortality were computed in three different Cox regression models: the first model contained only sex and diabetes as main effects, the second also contained age classes while the third had the number of concomitant medications, previous cardiovascular events and interaction between diabetes and age classes, diabetes and number of concomitant medications, diabetes and previous events too.

The number of concomitant medications did not include anti-diabetic treatment, and previous hospitalization referred to the preceding three years (CHD and MI admission for previous CHD events, CVD and stroke for previous CVD events, HF for previous HF events, mortality for previous CHD, CVD and HF events).

The odds ratios (ORs) for females with diabetes compared to males with diabetes treated with anti-diabetic or cardiovascular drugs were analyzed using logistic regression models adjusting for age classes and number of concomitant medications, excluding anti-diabetic treatment in the former and excluding anti-diabetic treatment and cardiovascular drugs in the latter.

The ORs of females with diabetes undergoing clinical exams compared to males were analyzed using logistic regression models adjusted for age class, number of concomitant medications (excluding anti-diabetic treatment) and previous cardiovascular events.

All analyses were done with Stata 12.0 (Stata Corp LP, College Station, Texas, USA) and JMP Pro 10.0 (SAS Institute Inc., Cary, NC, USA).