Gender differences in the relationship between diabetes process of care indicators and cardiovascular outcomes

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Background: Adherence to recommended guidelines in the care for diabetes has been demonstrated to significantly prevent the excess risk of hospitalization and mortality for cardiovascular diseases. Aim of this study was to evaluate whether adherence to a standardized process quality-of-care-indicator in diabetes, is able to predict, equally in men and women, first hospitalization or mortality risk after acute myocardial infarction (AMI), ischemic stroke (IS), congestive heart failure (CHF), lower extremity amputations (LEA) or any of above major adverse cardiovascular events (MACE). Methods: Guideline composite indicator (GCI), a process indicator including one annual assessment of HbA1c and at least two among eye examination, serum lipids measurement and microalbuminuria, was measured in the year 2006 in 91,826 (46,167 M/45,659 F) diabetic patients, living in Tuscany (Italy). By a Cox-proportional hazard regression model, the effect of GCI adherence was assessed on hospitalization mortality risk for AMI, IS, CHF, LEA and MACE in both genders in a follow-up period of 6 years (2007–12). Results: After adjusting for covariates, adherence to CGI exerted a significant positive effect on AMI, CHF and LEA outcomes among men, whereas among women, GCI adherence significantly decreased hospitalization risk only for CHF and mortality risk after IS. Finally, GCI adherence significantly reduced hospitalization risk for MACE of about 15% and 11% in men and women, respectively. On the contrary, GCI adherence seemed to have no significant influence on mortality risk after hospitalization for MACE in both genders. Conclusion: In this cohort, over a 6-year follow-up, GCI adherence was found to be a significant predictor of lower cardiovascular risk, with some evident gender differences.

Introduction

Diabetes greatly increases the risk of hospitalization and mortality due to cardiovascular events, and both organizational factors and adherence to recommended guidelines in the care for diabetes have been demonstrated to significantly prevent this excess risk. However, up until now, what remains unclear is whether a measure of compliance to screening guidelines significantly predicts the risk of cardiovascular outcomes (hospitalization or mortality) equally in diabetic men and women.

Gender differences, as a matter of fact, do exist in the relation between diabetes and the incidence of cardiovascular disease. Diabetes-associated risk of acute myocardial infarction (AMI) or ischemic stroke (IS) seems to be greater in women than in men, and, additionally, the probability of major outcomes (i.e., readmissions and mortality) after acute cardiovascular events is higher for diabetic women than for their male counterparts. Nonetheless, to the best of our knowledge, the reasons for this gender difference are poorly understood. In addition to previously suggested explanations for this difference, we deem it plausible that adherence to guidelines exerts a different cardiovascular protective effect in diabetic women, when compared with men.

In light of the discussion above, this study aims at evaluating whether the relationship between adherence to guidelines and

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Guideline composite indicator

219
cardiovascular outcomes differs between males and females in a population of diabetic patients from the Tuscany region, Italy.

Methods

Population

The study population composed of all residents of Tuscany identified as diabetic in the year 2006 and then retrospectively followed since 1 January 2007 up until 31 December 2012. Diabetic patients were selected based on whether they satisfied any of the following criteria: (i) had been discharged from any hospital in Tuscany with primary or secondary ICD-9-CM codes of diabetes (ICD-9 codes 250.xx); (ii) were given at least two prescriptions of anti-diabetic drugs (ATC class A10A or A10B) and (iii) had received a certified diagnosis of diabetes. This information was gathered from a regional dataset, which also included information on the prescription of drugs; diabetes-related consumables, clinical chemistry examinations and prescriptions for specialist consultations, all of which are exempt from out-of-pocket expenditure in Tuscany. This regional dataset is fully reliable since 1 January 2005 and captures almost the whole resident population of known diabetic patients. Considering that in Tuscany all citizens are entitled to have free universal access to diabetes care, we can reliably exclude presence of any medical care outside the public health services.

To better homogenize the baseline risk of cardiovascular events and of compliance to guidelines, all alive patients not being treated with glucose-lowering drugs in year 2006 were excluded from the cohort. Drug prescription, indeed, permitted to assure at least one yearly chance of contact with either general practitioners or diabetes specialists.

Data

The outcomes of interest were (i) hospitalization with primary or secondary ICD-9-CM diagnosis code of AMI (ICD-9-CM codes 410.xx) or IS (ICD-9-CM codes: 430.xx, 431.xx, 432.xx, 434.xx or 436.xx) or congestive heart failure (CHF) (ICD-9-CM codes: 401.91, 402.01, 402.11, 402.91, 404.01, 404.13, 404.93, 428.0, 428.1, 428.9) or lower extremity amputation (LEA) intervention (ICD-9-CM procedure codes: 84.1x) and (ii) all-cause mortality defined as a death for any cause occurring during or after first hospitalization for any of the aforementioned cardiovascular events. Each hospitalization was then assigned to a disease cohort based on the above stated diagnosis codes. When multiple hospitalizations for the same condition occurred, only the first event was considered. Additionally, patients hospitalized in the years 2005 and 2006 for the same disease condition of the outcome were excluded. In each analysis, however, a covariate concerning the burden of previous hospitalizations due to other cardiovascular events than the one considered has been added, coded as a dummy (0, absence; — presence).

Finally, with the term MACE (major adverse cardiovascular events), we considered either any first hospitalization or mortality after hospitalization for AMI or IS or CHF or LEA.

For each patient, the following composite indicator of compliance to recommended diabetes guidelines was calculated: the guideline composite indicator (GCI), a dummy variable (0, 1) indicating one assessment of glycated hemoglobin (HbA1c) and at least two assessments among eye examinations, serum lipid profile and microalbuminuria in the year 2006.7,18 Finally, for each selected patient, information was obtained for the following variables: age, sex, Charlson Comorbidity Index,19 type of glucose-lowering drug (assuming value one if insulin only, two if oral agents and insulin and three if oral agents only), Drug Prescription Index (DPI), a dummy variable (0, 1), indicating whether each diabetic patient received at least two prescriptions among angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs), aspirin or statins in year 2006. GCI fulfilment, as well as DPI or antidiabetic therapy were evaluated in the year 2006. After having excluded all patients who died in 2006, the observational period started on 1 January 2007 and ended on 31 December 2012. Consequently, for each outcome, a censoring time variable was created, corresponding to the date of the first hospitalization for the cardiovascular event or to the date of death after hospitalization or to 31 December 2012 if the patient was alive at that date and had no hospitalizations over the period of the study.

Data were anonymized at the Regional Health Information System Office where each patient was assigned a unique identifier that was the same for all administrative databases. This identifier does not allow to disclose the patient’s identity and other sensitive data. The study was carried out in compliance with the Italian law on privacy, and approval by an Ethics Committee was not required.

Statistical analysis

First, baseline characteristics were compared between diabetic men and women using a Chi-square test for discrete variables and Wilcoxon rank sum test for continuous variables. Second, the diabetic population alive at 1 January 2007 was followed for 6 years until 31 December 2012 to estimate the risk of any of the previously defined cardiovascular outcomes by a Cox proportional hazard model. Age, Charlson Index, local health care area unit, GCI, DPI and antidiabetic therapy were included in the models as covariates to measure the impact of compliance to guidelines (GCI) on outcomes in both men and women, while holding the other predictors at a constant level. For each Cox regression, we performed the test of proportional-hazards assumption,20 which was not significant suggesting that the proportional hazard assumption was met.

Finally, the hazard function for hospitalization after MACE was evaluated by Kaplan–Meier cumulative hazard graph analysis.

In all the analyses, a P value of <0.05 was considered significant, and confidence intervals were calculated at 95%. All analyses were performed using SAS for Windows Ver. 9.3 (SAS Institute, Cary, NC) and STATA Ver. 13 (College Station, TX).

Results

The study cohort at baseline consisted of 91,826 diabetic patients, of whom 46,167 (50.3%) were males and 45,659 (49.7%) females. Characteristics of the sample were in line with an Italian study based on administrative care data.21 Women were on average significantly older than men, with a higher prevalence in age above 65 years and with a lower burden of co-morbidities as described by the Charlson Comorbidity Index (table 1). The compliance to guidelines as measured by a positive GCI value was slightly higher among women than among their male counterparts (30.1% vs. 29.2%; P = 0.004). Both oral and insulin therapy were prescribed more often to men than to women except for the combined therapy of insulin and oral antidiabetic drugs, which was more frequently prescribed to women (table 1). Prescription of ASA was more frequent among men, while ACEI/ARBs were prescribed more to women (table 1). All these differences were significant at 5%. The population under study has been moreover stratified by privacy, and approval by an Ethics Committee was not required.
Over the six years of observation, there have been 2837 first hospitalizations for AMI, 3465 for IS, 2182 for CHF and 522 for LEA, whereas post-hospitalization deaths were 380 for AMI, 413 for IS, 471 for CHF and 102 for LEA (table 3). Over this same period, the total number of MACE (first hospitalization or mortality after hospitalization for any considered cardiovascular event, excluding, each time, patients with previous hospitalizations for that specific event but including those with hospitalizations for the other cardiovascular events) was 9286.

The Cox proportional hazard regression analysis, carried out separately in each gender, showed that in the male diabetic cohort, adherence to GCI was inversely related to the risk of first hospitalization and overall mortality for AMI (table 3). Similarly, GCI was significantly related to the adjusted risk of first hospitalization for CHF and for LEA. On the contrary, no significant association was found between GCI and the risk of any outcome related to IS (table 3).

In the cohort of diabetic women, in contrast with men, GCI did not seem to be associated with the risk of any of the outcomes for AMI, whereas the higher the compliance to GCI, the lower the risk of first hospitalization for CHF as well as for mortality after hospitalization for IS (table 3).

Results from Cox regression analysis, after adjusting for the covariates (age, health area unit, antidiabetic therapy, Charlson index, DPI and previous cardiovascular burden), showed that hospitalization after MACE was significantly reduced in presence of compliance to GCI in both men and women. This result is also confirmed by the Kaplan–Meier analysis (figure 1). On the contrary, the risk of mortality after hospitalization for MACE was not associated to GCI compliance in both genders (figure 2).

Discussion

Risk management has an important role in improving the prognosis of cardiovascular complications in diabetic patients. In this context, it has been suggested that a lower compliance to screening guidelines, other than being associated with a poorer quality of care, is associated with higher cardiovascular morbidity and mortality. Adherence to recommended diabetes care guidelines, as indexed by GCI, has been used in Italy, as an indicator of care process quality, in studies performed with administrative databases and designed for investigating the performance of different models of diabetes care delivery.

Compared with a previously Italian study using this same index, the rates of assessments of each single GCI item, i.e. HbA1c, eye examination and plasma lipids measurement were quite similar, while full compliance to GCI was a little greater than in this study—35.8% versus 30.1% respectively; thus, highlighting the fact that large opportunities remain for improvement in diabetes care quality in these populations.

Principal results of our study confirmed that GCI is a reliable predictor of risk for cardiovascular events in diabetes, although with differences across gender and across selected cardiovascular events.

Full compliance to GCI resulted inversely related to the adjusted risk outcomes after AMI, only in men. This result might be the consequence of worse past metabolic control, poorer quality of diabetes care, delayed diagnosis of diabetes and higher comorbidity in diabetic women, particularly in post-menopausal age, with respect to males. It is interesting to highlight that among women, differently from men, full compliance to GCI was associated with a greater previous burden of cardiovascular events (table 2), further suggesting that in the female cohort all preventive measures, according to guidelines, are presumably adopted later than in men.

On the contrary, the consistent inverse relationship between compliance to guidelines and the excess risk of LEA related to diabetes as observed only among men may simply be explained by a much higher risk of this event in diabetic males than in female counterparts.

With respect to IS, adherence to GCI seems to have no significant effect on the likelihood of either hospitalization or of all-event

### Table 1 Characteristics of diabetic population under study at index baseline year 2006

<table>
<thead>
<tr>
<th></th>
<th>Males (N=13 485)</th>
<th>Females (N=32 682)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>66.6 ± 11.8</td>
<td>70.1 ± 12.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prescription of aspirin (%)</td>
<td>29.2</td>
<td>23.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prescription of statins (%)</td>
<td>27.5</td>
<td>19.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prescription of ACE inhibitors/ARB (%)</td>
<td>51.4</td>
<td>44.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>DPI (%)</td>
<td>32.5</td>
<td>24.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Charlson Index ≥ 2 (%)</td>
<td>33.8</td>
<td>31.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Insulin therapy (%)</td>
<td>23.6</td>
<td>18.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oral therapy (%)</td>
<td>21.7</td>
<td>17.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous CV events N (%)</td>
<td>1710 (11.2)</td>
<td>3675 (12.7)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

### Table 2 Characteristics of diabetic population under study at index baseline year 2006, stratified by gender and adherence to GCI

<table>
<thead>
<tr>
<th></th>
<th>Males (N=13 485)</th>
<th>Females (N=32 682)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>66.6 ± 11.7</td>
<td>66.6 ± 11.9</td>
<td>NS</td>
</tr>
<tr>
<td>Prescription of aspirin (%)</td>
<td>29.2</td>
<td>23.9</td>
<td>0.0001</td>
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</tr>
</tbody>
</table>

a: Tested by chi-square test or by two-tailed Wilcoxon rank sum test. NS = not significant.
outcome equally in men and women. This result might be due to the fact that IS pathogenesis is, as widely known, strongly correlated to a panel of several different co-morbidities (high blood pressure, atrial fibrillation, etc.) other than to diabetes. The only exception was the risk of mortality after IS hospitalization, which appeared inversely related to GCI in women [hazard ratio: 0.673 (0.469–0.948); P = 0.0275]. This result might be due to the higher risk of mortality for IS in women than in men which is associated with poor quality of diabetes care, a late diagnosis of diabetes, a higher rate of stroke recurrence or a worse interaction with poor glycaemic

Table 3 Six-year adjusted risk of cardiovascular events’ clinical outcomes in diabetic patients, stratified by gender and expressed as HR (95% CI), as predicted by the GCI, evaluated on index year 2006

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AMI</th>
<th>IS</th>
<th>Congestive heart failure</th>
<th>Lower extremity amputations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR (95% CI)</td>
<td>N</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Males (N = 46,167)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First hospitalization</td>
<td>1673</td>
<td>0.843 (0.755–0.941) (0.0025)</td>
<td>2016</td>
<td>0.939 (0.851–1.036) (NS)</td>
</tr>
<tr>
<td>Mortalityb</td>
<td>181</td>
<td>0.675 (0.466–0.959) (0.0323)</td>
<td>201</td>
<td>0.744 (0.531–1.029) (NS)</td>
</tr>
<tr>
<td>Females (N = 45,659)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First hospitalization</td>
<td>1164</td>
<td>0.969 (0.850–1.103) (NS)</td>
<td>1449</td>
<td>0.980 (0.872–1.100) (NS)</td>
</tr>
<tr>
<td>Mortality</td>
<td>199</td>
<td>1.001 (0.718–1.378) (NS)</td>
<td>212</td>
<td>0.673 (0.469–0.948) (0.0275)</td>
</tr>
</tbody>
</table>

HR, hazard ratio adjusted for age, Charlson Index, Local Health Area Unit, DPI and type of antidiabetic therapy.

a: Number of events.  
b: Mortality after first hospitalization.  
c: P value.

Figure 1 Graphs display the Kaplan–Meier cumulative hazard of first hospitalization after MACE in diabetic population with full compliance to GCI (GCI = 1, when compared with GCI = 0), stratified by gender, after adjusting for the same covariates used in the final Cox multivariable model.
outpatients’ national database of the Italian diabetic population. 27 Women, moreover, seem to be more exposed to all-cause-short term mortality risk after stroke, most likely because of the combined impact of older age, differences in clinical presentation and of worse access to adequate therapies or diagnostic procedures when compared with men.34,35 As to the older age of women, our finding is in agreement with what reported by a large outpatients’ national database of the Italian diabetic population.27

As to CHF, the excess risk attributable to diabetes, when compared with non diabetic population, was similar in both males and females: hazard ratio: 2.631 (2.499–2.769) versus 2.550 (2.418–2.688); P = NS and, interestingly, in this balanced condition, the adherence to GCI seems to have a similar protective role from hospitalization independent of gender.

The above results, showing an overall disadvantage of women with respect to men, especially toward AMI outcomes, are somewhat diluted when considering MACE. Indeed, for first hospitalizations, protection from GCI adherence was only marginally greater in men than in women: 15% versus 11%, respectively, whereas adherence to GCI seemed not to be significantly associated with the risk of a more severe and advanced event such as mortality after hospitalization. Because of the lack of reliable diabetic registries in our country, it is not possible to have affordable comparisons of the mortality rate with respect to similar populations and comparisons are further complicated since in this study we consider only treated diabetic patients. It should be, however, noted that yearly all-cause mortality rate was comparable with that of a previous Italian study.28

Finally, the compliance to GCI’s items assumes an even more relevant predictive value, since all progressive hazard regression models have been adjusted for DPI and for recommended drug therapy for the prevention and treatment of cardiovascular outcomes.

Limitations and strengths of the study

The main limitation of this study is its use of administrative databases, which although widely available at reasonable cost, do not provide information on clinical covariates. A further limitation is the impossibility of any clear-cut distinction between type 1 and type 2 diabetic patients, although the advanced mean age of these patients suggests that type 2 diabetes covers the overwhelming percentage of the population.

This study, however, has some important strengths. First, it is based on observational data from a region counting about 3.6 million residents. Moreover, the Italian National Health System follows a ‘Beveridge model’, which provides universal healthcare coverage through general taxation. All the residents are therefore entitled to have free access to the same level of care, and therefore, we hypothesize that the baseline cardiovascular risk exposure in our study population is homogeneous. Nonetheless, it is worth noticing that only about one third of the diabetic residents were found to adhere to the screening clinical guidelines, as expressed by GCI. Finally, the study relies on an adequate extension of follow-up (6 years) and it also includes information on drug therapies.

In summary, this study confirms previous results that compliance to GCI, a process index based on a standardized panel of quality-of-care indicators, significantly predicts the risk of cardiovascular outcomes in diabetic populations. However, this study adds a novel finding to what has been previously observed: the strength of the relationship between compliance to guidelines and the cardiovascular outcomes depends on gender and on the specific cardiovascular diseases. The inverse relation between adherence to GCI and outcomes after AMI was evident only among men, reflecting an overall reduced sensitivity of women to the protective effect exerted by GCI. This could be a further reason, among many others, to explain the higher diabetes-related excess risk of coronary heart disease among women. Prediction of overall mortality after IS seems related with poor GCI adherence only in women; on the contrary, the risk of LEA was related to GCI only among men.

These results have implications for research analysing the relationship between adherence to guidelines and outcomes in patients with diabetes, clearly indicating that compliance to GCI can be profitably used as a valuable predictive marker of clinical outcomes in diabetic populations. Process indicators such as GCI and DPI are indeed monitored annually in the performance evaluation system of Tuscan healthcare system.57 Furthermore, these findings contribute to raise awareness among healthcare professionals and policy makers towards gender-sex aspects in the definition of guidelines indicators and in the clinical gender-oriented approach to the care of diabetes. However, whether these differences are completely explained by a sex dimorphism or by a reduced attention toward gender in the treatment of diabetes and its complications remains to be fully clarified.

Acknowledgements

Data from this study were preliminarily presented as a poster at the 50th EASD Annual Meeting, Vienna, Austria, 15–19 September 2014.
Conflicts of interest: None declared.

Key points

- A composite indicator of compliance to recommended diabetes guidelines (guideline composite indicator [GCI]) significantly predicts the risk of cardiovascular outcomes (hospitalization or post-event mortality) in diabetic patients.
- The extent of outcome risk prediction by GCI in these subjects is, however, significantly different for any cardiovascular event and between genders.
- These findings contribute to raise awareness among healthcare professionals and policy makers towards gender-sex aspects in the definition of guidelines indicators for diabetes, when tested in population studies.

References