

Estimating the real burden of cardiovascular mortality in diabetes

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Abstract. – OBJECTIVE: To compare different methods assessing the burden of cardiovascular mortality in diabetes mellitus, which is usually underestimated by standard mortality statistics based on the underlying cause of death.

PATIENTS AND METHODS: All residents in the Veneto Region (Italy) aged 30-89 years with co-payment exemption for diabetes in January 2010 (n=185,341) were identified and linked with mortality records (2010-2015). The underlying causes of death, as well as all the diseases mentioned in the death certificate (multiple causes), were extracted. The standardized mortality ratios (SMR) were computed with regional rates as a reference.

RESULTS: After grouping diabetes and circulatory diseases as the underlying cause of death, the mortality rates were highly increased, especially among patients aged 30-54 years: SMR 4.24 (95% confidence interval 3.57-5.00) and 9.84 (7.47-12.72) in males and females, respectively. After re-assignment of the underlying cause in deaths from diabetes, the percentage of overall mortality caused by circulatory diseases increased from 33.8% to 41.7%. Based on multiple causes, the risk of death was increased for several cardiovascular diseases, including causes rarely emerging from standard mortality statistics such as atrial fibrillation/flutter.

CONCLUSIONS: The re-assignment of the underlying cause and the analyses of the multiple causes of death allowed to estimate the whole burden of mortality associated with cardiovascular diseases.

Key Words:

Mortality, Diabetes, Cardiovascular diseases.

preventive interventions, and monitor specific mortality patterns of subjects affected by chronic diseases such as diabetes mellitus¹.

Traditionally, in patients with diabetes the major cause of morbidity and mortality is represented by cardiovascular diseases². In recent years, among subjects with diabetes, a large decline in the proportion of deaths from vascular causes has been observed, partially offset by an increase in the proportion of deaths from non-vascular and non-cancer causes³. However, multiple intricacies arise when mortality records are analyzed in diabetic subjects. First, diabetes itself is selected as the cause in over 10% of deaths among affected patients^{3,4}. It must be remarked that the standard mortality statistics are based on the underlying cause of death (UCOD), which is identified from all the diseases reported in the death certificate according to internationally adopted algorithms⁵. For example, according to the existing coding rules, diabetes is selected as the UCOD when reported in the death certificate as a cause of ischemic heart or cerebrovascular diseases^{5,6}, leading to an underestimation of the burden of mortality associated with the latter conditions. Second, with the ageing of both the general and the diabetic populations, the associated burden of multiple comorbid conditions is steadily increasing. As a consequence, there may be no simple etiological chain leading to the identification of a single underlying cause; instead, death often is the result of a complex interaction between multiple factors¹.

In order to properly investigate mortality data at the population level, an option might be to analyze deaths from diabetes and circulatory diseases both separately, as well as grouped as cardiometabolic diseases⁷. Nonetheless, in order to fully investigate mortality rates associated with cardiovascular causes in diabetes, multiple methods might be adopted, including the re-as-

Introduction

Routinely collected cause-specific mortality data are used to describe the health profile of populations, evaluate the impact of risk factors,

signment of the cause when the selected UCOD is diabetes itself, and the analysis of all the diseases reported in death certificates (the so-called multiple causes of death – MCODE-approach). This study aims at estimating the whole burden of cardiovascular mortality in a large population-based cohort of subjects with physician-diagnosed diabetes.

Patients and Methods

Identification and Follow-Up of the Cohort

Mortality was investigated in diabetic patients identified from the regional archive of subjects with copayment exemption for diabetes in the Veneto Region (North-Eastern Italy). The details have been previously published⁴. Briefly, we identified all residents aged 30-89 years with copayment exemption for diabetes in January 2010, and linked them with the archive of causes of deaths occurring in the period 2010-2015. Each subject was followed up from January 1st, 2010, until death, or 90 years of age, or December 31st, 2015, whichever came first. Regional health records were routinely submitted to a standardized anonymization process that assigned a unique code to each subject allowing record linkage between electronic archives, without any possibility of back-retrieving the subject's identity. Since all analyses were carried out on routinely collected anonymized records, the study was deemed exempt from approval by the Local Ethics Committee.

Assignment of Cardiovascular Causes of Death

The regional archive of causes of death not only includes the UCOD, but also all diseases mentioned in the death certificate (MCOD), coded according to the International Classification of Diseases, 10th Edition (ICD-10). The UCOD is selected by means of the Automated Classification of Medical Entities, a computer program developed by the US National Center for Health Statistics to standardize the assignment of the underlying cause⁸.

The first step to assess cardiovascular mortality in the cohort was to group the deaths from diabetes (ICD-10 codes E10-E14) and circulatory diseases (I00-I99), selected as the UCOD. According to the ICD-10, diabetes is classified further based on the presence of specific complications: periph-

eral vascular disease (last character of the ICD-10 code = 5), other specified, unspecified, or multiple complications (last character 0-4, 6-8), and diabetes without complications (last character 9). Diabetes with the peripheral vascular disease was directly classified among cardiovascular deaths. Furthermore, in the case of deaths from diabetes without complications, the cause of death was re-assigned by running the ACME program after deleting diabetes from the list of diseases mentioned in the death certificate. Through this UCOD-based methodology, a more complete estimate of the overall burden of mortality from circulatory diseases and specific disorders including hypertensive diseases, ischemic heart diseases, cerebrovascular diseases, cardiac valve disorders, cardiomyopathy, atrial fibrillation and flutter, and peripheral vascular diseases, could be achieved. Lastly, any mention of the above cardiovascular diseases in the death certificate (MCOD) was further analyzed, irrespective of their selection as the UCOD.

Statistical Analysis

The proportional mortality from cardiovascular disorders (share of deaths from all causes) was compared between the routinely selected UCOD, the UCOD resulting from the re-assignment of deaths from diabetes, and the MCODE approach.

Furthermore, Standardized Mortality Ratios (SMRs) with 95% confidence intervals (CIs) based on the Poisson distribution were computed as the ratios between deaths observed in the cohort and those expected according to age and gender-specific regional mortality rates. SMRs for the main cardiovascular disorders were computed based both on the UCOD and the MCODE.

Results

Among 185,341 subjects with diabetes included in the cohort, 36,382 died during the follow-up period: diabetes was selected as the UCOD in 4,518 decedents (12.4%), and a circulatory disease was selected in 12,282 (33.8%). After grouping the two nosologic categories, rate ratios were highly increased compared to the overall regional population, especially among younger female subjects (Figure 1): the estimated SMR among patients aged 30-54 years were 4.24 (95% confidence interval 3.57-5.00) and 9.84 (7.47-12.72) in males and females, respectively.

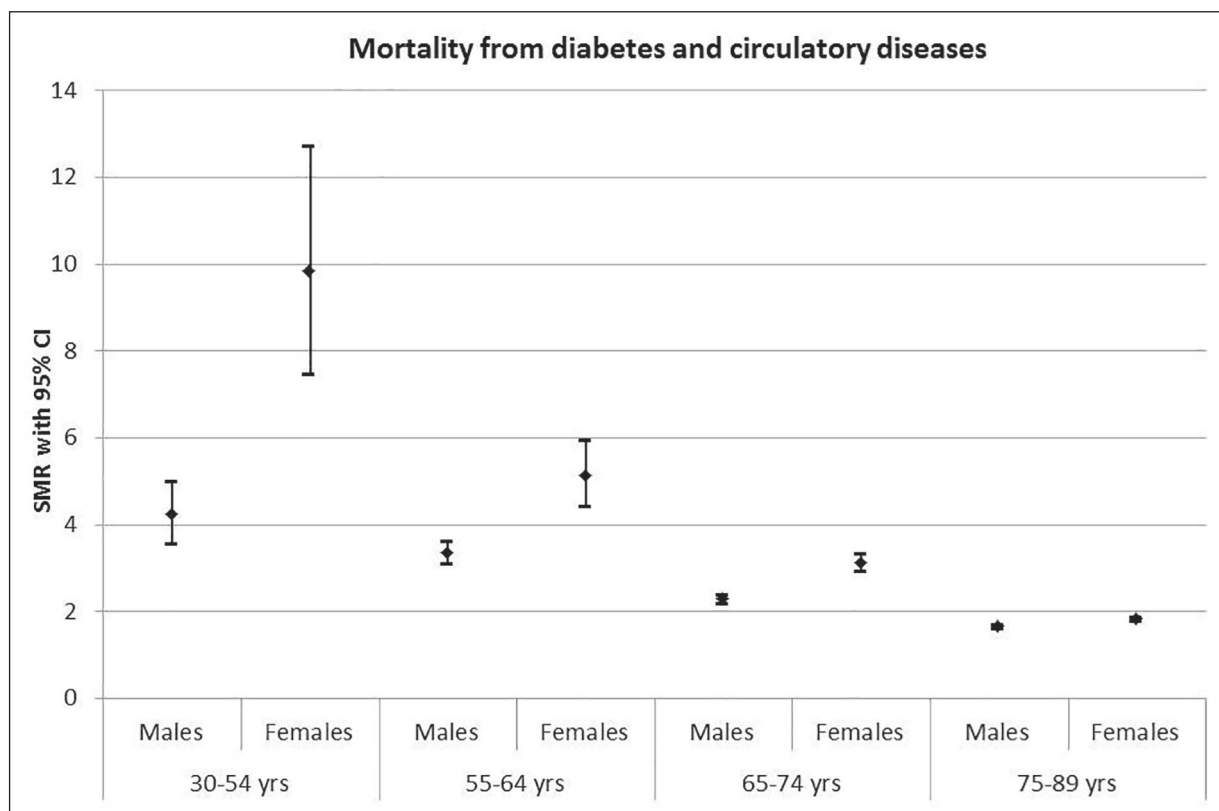


Figure 1. Standardized mortality ratio (SMR) with 95% confidence interval (CI) for mortality from diabetes and circulatory diseases, by gender and age class. Reference = expected deaths based on gender- and age-specific mortality rates in the Veneto region (Italy), 2010-2015.

Out of all deaths observed in the cohort, 2.1% were caused by diabetes with peripheral vascular disorders, and 6.6% were caused by unspecified diabetes re-assigned to circulatory diseases after applying the coding rules without accounting for the mention of diabetes. As a result, the percentage of deaths with circulatory diseases as the underlying cause increased from 33.8% to 41.7%, with a larger share in the female (Figure 2). Ischemic heart diseases, the most frequent nosologic category, increased from 14.0% to 16.9% of all deaths after re-assignment of the UCOD.

Table I shows the distribution of the routinely assigned UCOD among deaths with ischemic heart diseases listed as a contributory cause, but not selected as the underlying one. A substantial percentage of deaths was originally coded as diabetes, mainly without specified complications. Most of these latter deaths could be attributed to ischemic heart diseases by using the above re-assignment process. Nonetheless, most of the deaths were distributed across several nosologic categories: cancer, other co-existing circulatory diseases (mainly cerebrovascular disorders), infectious, neurologic,

respiratory, or digestive diseases. In these cases, only the MCOD approach allowed the assessment of the contributory role of ischemic heart disorders in the process leading to death.

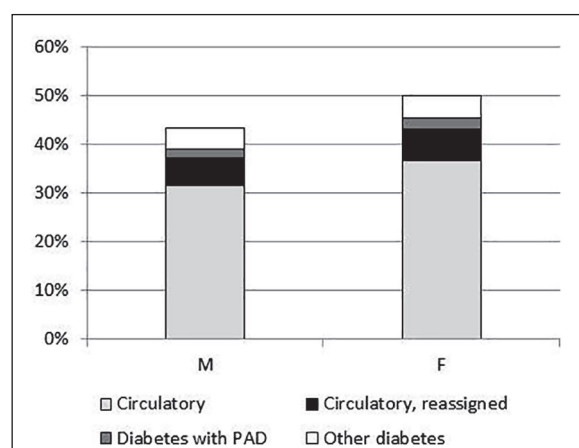


Figure 2. Underlying cause of death among 36,382 patients with diabetes: percentage of circulatory causes, diabetes with peripheral vascular disease (PAD), diabetes with other complications, and circulatory diseases resulting from the re-assignment of cause of death in unspecified diabetes.

Table I. Underlying cause of death selected in 4,988 certificates of diabetic subjects with ischemic heart disease mentioned as a contributory cause.

Underlying cause (ICD-10 codes)	No.	%
Common infections (A00-B99/B15–B19 excluded/, J10–J22, J69, J85–J86, N10–N12, N136, N15, N390)	322	6.5
Neoplasms (C00-D48.9)	1214	24.3
Diabetes (E10-E14)	1787	35.8
With peripheral circulatory complications (x.5)	270	5.4
With other complications (x.0-x.4, x.6-x.8)	296	5.9
Without complications (x.9)	1221	24.5
Mental and nervous system disorders (F00-G99)	216	4.3
Circulatory diseases (I00-I99)	643	12.9
Cerebrovascular diseases (I60-I69)	367	7.3
Chronic obstructive pulmonary disease	144	2.9
Diseases of the digestive system (K00-K93)	252	5.0

By means of the MCOD approach, a large burden of mortality associated with ischemic heart diseases, hypertensive diseases, and cerebrovascular diseases could be assessed (Table II). Causes such as atrial fibrillation/flutter which were rarely selected as the UCOD, were frequently mentioned in death certificates of diabetic patients. Furthermore, the role of cardiac valve disorders and peripheral vascular diseases was much more evident with this approach.

Table III shows that for all analyzed circulatory diseases, SMR estimates based on MCOD were higher than those based on the underlying cause. The only exception was represented by peripheral vascular disorders, which already showed considerably increased risks after the inclusion of the specific diabetic complication codes (E1x.5). As regards atrial fibrillation/flutter, a significantly increased SMR could be observed only through the analyses of MCOD. Risk estimates based on

both the underlying, as well as multiple causes of death, were consistently higher in females compared to males.

Discussion

The present study shows that the impact of cardiovascular diseases on mortality in subjects with diabetes is still large, and might be underestimated by the analysis of routinely collected mortality statistics. To overcome this limitation, the first approach was to combine the causes of death (cardiometabolic diseases), followed by re-assignment of cardiovascular causes in order to disentangle the complexity of diabetes and cardiovascular diseases in the death process. Through this methodology, a more complete estimate of the whole cardiovascular risk in diabetes could be obtained.

Table II. Number of deaths from circulatory causes (n) and share of deaths from all causes (%) according to the underlying cause of death (UCOD), to the re-assignment of the underlying cause, and to multiple causes of death (MCOD).

	UCOD		UCOD reassigned		MCOD	
	n	%	n	%	n	%
All circulatory causes (I00-I99)	12282	33.8	15174*	41.7	–	–
Hypertensive diseases (I10-I15)	1261	3.5	1692	4.7	7606	20.9
Ischemic heart diseases (I20-I25)	5085	14.0	6146	16.9	10073	27.7
Cerebrovascular diseases (I60-I69)	2707	7.4	2989	8.2	5803	16.0
Cardiac valve disorders (I05-I08, I34-I38)	600	1.6	633	1.7	1665	4.6
Cardiomyopathy (I42)	333	0.9	353	1.0	713	2.0
Atrial fibrillation and flutter (I48)	295	0.8	339	0.9	3492	9.6
Peripheral vascular disorders (I70.2, I73)	125	0.3	867*	2.4	1660*	4.6

*Codes E1x.5 included.

Table III. Number of deaths (n) and standardized mortality ratio (SMR) with 95% confidence interval (CI) in a cohort of 185,341 patients with diabetes according to the underlying cause (UCOD) and to multiple causes of death (MCOD). Reference = expected deaths based on gender and age-specific mortality rates in the Veneto region (Italy), 2010-2015

	UCOD		MCOD	
	n	SMR (CI)	n	SMR (CI)
Males				
Hypertensive diseases (I10-I15)	559	1.21 (1.11-1.32)	3951	1.74 (1.68-1.79)
Ischemic heart diseases (I20-I25)	3058	1.72 (1.66-1.79)	6268	1.97 (1.92-2.02)
Cerebrovascular diseases (I60-I69)	1360	1.42 (1.35-1.50)	3025	1.56 (1.50-1.62)
Cardiac valve disorders (I05-I08, I34-I38)	239	1.36 (1.20-1.55)	759	1.51 (1.41-1.63)
Cardiomyopathy (I42)	244	1.73 (1.52-1.96)	517	1.89 (1.73-2.06)
Atrial fibrillation and flutter (I48)	105	1.02 (0.84-1.24)	1791	1.39 (1.33-1.46)
Peripheral vascular disorders (I70.2, I73, E1x.5)	480	3.69 (3.37-4.03)	995	3.09 (2.90-3.29)
Females				
Hypertensive diseases (I10-I15)	702	1.30 (1.20-1.40)	3655	1.81 (1.75-1.87)
Ischemic heart diseases (I20-I25)	2027	1.93 (1.85-2.02)	3805	2.19 (2.12-2.26)
Cerebrovascular diseases (I60-I69)	1347	1.39 (1.32-1.47)	2778	1.58 (1.52-1.64)
Cardiac valve disorders (I05-I08, I34-I38)	361	1.63 (1.47-1.81)	906	1.78 (1.66-1.90)
Cardiomyopathy (I42)	89	1.65 (1.32-2.02)	196	1.87 (1.62-2.15)
Atrial fibrillation and flutter (I48)	190	1.52 (1.32-1.76)	1701	1.58 (1.51-1.66)
Peripheral vascular disorders (I70.2, I73, E1x.5)	383	4.30 (3.88-4.75)	665	3.74 (3.46-4.04)

When diabetes and circulatory diseases, selected as the UCOD, were grouped, they had a profound impact on mortality, especially in the younger age class (30-54 years). The present findings confirm the higher proportional increase in the risk for cardiovascular deaths in females, especially among younger patients⁹. The re-assignment process of the UCOD led to a roughly 20% increase in the proportion of deaths attributed to cardiovascular diseases overall, and specifically to nosologic categories such as ischemic heart diseases. Moreover, the MCODE approach allowed to fully assess the impact of several cardiovascular diseases as the cause of death.

Peripheral vascular disorders confirmed their impressive impact on the mortality risk in patients affected by diabetes¹⁰. Furthermore, the impact was assessed for less frequent cardiovascular causes such as cardiac valve disorders, cardiomyopathy, and atrial fibrillation/flutter, both in males and females. In particular, the prevalence of persistent atrial fibrillation is increased in type 2 diabetes¹¹, and conversely diabetes represents a risk factor for mortality among patients with atrial fibrillation^{12,13}. However, the role of atrial fibrillation may be underappreciated by analyses based only on the UCOD. In the present study, atrial fibrillation/flutter was rarely selected as the UCOD, but was mentioned in nearly 10% of death certificates among diabetic subjects. The MCODE analysis showed a significant increase in the risk

of death associated with atrial fibrillation compared to regional reference rates.

The present study has different strengths: standardized coding of death certificates, the large number of subjects, and the use of both UCOD and MCODE for classifying the cardiovascular causes of death. The limitations of the study are the lack of distinction between type 1 and type 2 diabetes and the absence of clinical variables such as the severity of diabetes. In fact, it has been recently demonstrated that type 2 diabetes patients who have not only glycated hemoglobin, but also additional cardiovascular risk factors (low-density lipoprotein cholesterol, albuminuria, smoking, and blood pressure) within target ranges, have similar rates of death and cardiovascular events as the general population¹⁴.

At a global level, it is estimated that cardiovascular diseases are responsible for about half of all deaths in the subjects with type 2 diabetes¹⁵. However, the data from several studies carried out in high-income countries suggest a decline in the mortality associated with cardiovascular diseases among people with diabetes¹⁶, possibly due to improvements in the control of cardiovascular risk factors¹⁷. In the US, from 1988-1994 to 2010-2015 the deaths from vascular causes declined from 44.5% to 30.9% of overall mortality among diabetic subjects³, mainly due to a decrease in deaths from ischemic heart and cerebrovascular diseases¹⁷. Nonetheless, due to the ageing of the diabet-

ic population and with the emergence of several vascular and non-vascular comorbidities (including renal disease, infections, and cancers)¹⁶, additional metrics are needed to measure the burden of mortality associated with the complications of diabetes.

Conclusions

In our view, the present data are important since they well suit the concept of multimorbidity, that is, the co-occurrence of multiple chronic conditions in the same person¹⁸. The patient with diabetes is emblematic in this respect, as he sums up many chronic cardiovascular complications that may act simultaneously. The multimorbidity dimension of diabetes may impact impressively on mortality, with many different conditions all of which may provide a relevant contribution to the risk of death¹⁹. Therefore, we suggest that additional approaches, including analyses of all conditions mentioned in the death certificates, should be adopted to estimate the real burden of cardiovascular mortality of this common disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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