Cardiovascular Complications Over 5 Years and Their Association With Survival in the GERODIAB Cohort of Elderly French Patients With Type 2 Diabetes

Diabetes Care 2018;41:156–162 | https://doi.org/10.2337/dc17-1437

Bernard Bauduceau,[1] Jean-Pierre Le Floch,[2] Serge Halimi,[3] Christiane Verny,[4] Jean Doucet,[5] and the SFD/SFGG Intergroup*

CARDIOVASCULAR AND METABOLIC RISK

OBJECTIVE

The GERODIAB study is a multicenter prospective observational study performed over 5 years in French patients aged 70 years or above with type 2 diabetes. This report deals with their cardiovascular complications and their relationship with survival.

RESEARCH DESIGN AND METHODS

Consecutive patients (n = 987, median age = 77 years) were included from 56 diabetes centers over 1 year. Individual characteristics, history and complications of diabetes, geriatric factors, and clinical and biological parameters were recorded. Survival was analyzed using the Kaplan-Meier method and proportional hazards regression models.

RESULTS

The frequency of cardiovascular complications increased from 47% at inclusion to 67% at 5 years. The most frequent complications were coronary heart disease (increasing from 30% to 41%) and vascular disease of the lower limbs (25% to 35%) and of the cerebral vessels (15% to 26%). Heart failure was less common, but its frequency doubled during the follow-up (9% to 20%). It was strongly associated with poor survival (P < 0.0001), as was vascular disease of the lower limbs (P = 0.0004), whereas coronary heart disease (P = 0.0056) and vascular disease of cerebral vessels (P = 0.026) had mild associations. Amputation (P < 0.0001) and foot wounds (P < 0.0001) were strongly associated with survival. In multivariate models, heart failure was the strongest predictor of poor survival (hazard ratio [HR] 1.96 [95% CI 1.45–2.64]; P < 0.0001). It remained significant when other factors were considered simultaneously (HR 1.92 [95% CI 1.43–2.58]; P < 0.0001).

CONCLUSIONS

Cardiovascular complications are associated with poor survival in elderly patients with type 2 diabetes, especially heart failure.

[1]Endocrinology, Bégin Hospital, Saint Mandé, France
[2]Diabetology-Endocrinology, Villecresnes Medical Hospital, Villecresnes, France
[3]Diabetology, Endocrinology, Grenoble Alpes University, Grenoble, France
[4]Gerontology, Bicêtre University Hospital, Le Kremlin-Bicêtre, France
[5]Internal Medicine, Geriatrics and Therapeutics, Saint Julien Hospital, Rouen University Hospital, Rouen, France

Corresponding author: Jean-Pierre Le Floch, jplefloch@dietvill.com.

Received 17 July 2017 and accepted 4 October 2017.

Clinical trial reg. no. NCT01282060, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1437/-/DC1.

*A complete list of the study investigators of the SFD/SFGG Intergroup can be found in the Supplementary Data online.

See accompanying articles, pp. 11, 14, 136, 143, and 150.

Diabetes is a great concern in aging people in Western countries, as approximately one-quarter of people over 65 years has diabetes, and more than one-third of patients with diabetes are aged 70 years or older (1,2). Diabetes is a well-known cause of cardiovascular complications and death (3,4). Cardiovascular complications of diabetes and their relationships with glucose control have been largely studied in younger patients with diabetes (5–7). Although the degenerative cardiovascular consequences of diabetes and aging accumulate in the elderly, similar studies have not been widely performed in large populations of elderly patients with diabetes (8).

The GERODIAB study is a multicenter, prospective, observational study that aims to describe the mortality in French patients aged 70 years and older with type 2 diabetes and its link with diabetes characteristics (9). In a previous report, we showed that cardiovascular complications were common at baseline in elderly patients with diabetes and were significantly associated with HbA_{1c}, geriatric disorders, and some individual characteristics (10).

The present report addresses the cardiovascular complications in the 987 patients of the GERODIAB cohort, their progression during the 5-year follow-up, and the associations of these factors with the 5-year mortality.

RESEARCH DESIGN AND METHODS

From June 2009 to July 2010, 987 consecutive ambulatory patients with type 2 diabetes (52.1% women) aged 70 years and over were included from 56 French diabetes centers. The centers were selected from voluntary French reference diabetes centers, after stratification of the French regional areas, using a random procedure. Patients with type 2 diabetes in France are usually managed by general practitioners (GPs) and are referred at least once a year to a regional reference center, especially for an annual checkup. The centers were chosen in order to include a total of 1,000 patients over 1 year. This number was estimated from previous epidemiologic data in order achieve a 90% power with a significant relative risk of 1.5 in the subgroup with high HbA_{1c}, and to provide a representative sample ≥0.1% of the French patients ≥70 years with type 2 diabetes. Ambulatory patients referred by their usual practitioners (mainly GPs) for an annual checkup or for specialized advice in ambulatory care were eligible. Included patients needed to be sufficiently autonomous, which was defined as having an activities of daily living score ≥3 (9,10). Patients had to give their consent to participate in the study after being fully informed. All consecutive eligible patients attending the center over 1 year were included in the study.

The main outcome of the study was death during the 5-year follow-up. A specific monitoring unit was used to get all the possible information concerning the death of the patients, including information derived from family, all the medical staffs managing the patients and especially GPs, and legal records. The following subjects were classified as "lost to follow-up": *1*) the patients without any available information on death and *2*) those who removed their consent to participate in the study (decision of our ethics committee). Clinical history of diabetes and associated diseases was recorded at inclusion. Due to the observational nature of the survey, management and follow-up measures were those defined in American, European, and French recommendations (11–13). They included HbA_{1c} level recorded at inclusion and then every 3 months, Modification of Diet in Renal Disease (MDRD) recorded at inclusion and then every 6 months, other laboratory parameters, ocular fundus examination, cardiac evaluation (including resting electrocardiogram [ECG]), and geriatric evaluation performed at inclusion and then every 12 months. Complementary explorations, including cardiovascular examinations, could be performed by investigators depending on the patients' needs and according to recommendations (11–13). As the study was noninterventional, the glycemic control objectives and treatments used were determined by the investigators according to recommendations. A more detailed description of the methodology has been presented previously (9,10).

Cardiovascular complications were diagnosed through the medical history, physical examination, and ECG, which were performed systematically every 6 months. Due to the observational nature of the study, complementary examinations were left to the discretion of the investigators, based on results of systematic assessments and according to the American and European/French guidelines for diabetes management (11–13). These included Doppler tests for lower limbs and cerebral vessels, echocardiography, computed tomography and angiography, and tests for silent ischemia. The patients had to agree to all the complementary tests.

Cardiovascular complications were classified based on clinical and complementary tests. Coronary heart disease was classified into three groups: *1*) myocardial infarction and acute coronary syndromes, if any evidence was found through history, ECG, or complementary examinations; *2*) angina pectoris, if evidence was found through history, ECG, or complementary examinations and there was no evidence for infarction; and *3*) no coronary heart disease otherwise (Table 1). Heart failure was classified as "yes" if evidence was found through clinical history or on complementary examinations (Table 1). Vascular disease of the lower limbs was classified into three groups: *1*) clinical, when evidence was found; *2*) subclinical, when evidence was found on clinical or complementary examinations, including hemodynamic stenosis on Doppler tests either performed during the study or recorded in the medical history of the patient; and *3*) no arterial disease otherwise (Table 1). Vascular disease of the cerebral vessels was classified into three groups: *1*) stroke when evidence was found; *2*) subclinical, when evidence was found on complementary examinations, including hemodynamic stenosis found on Doppler tests either performed during the study or recorded in the medical history of the patient; and *3*) no arterial disease otherwise. Reversible cerebrovascular involvement (transient attack) was based on the clinical history and was grouped with subclinical abnormalities (Table 1). The cumulative grade of each type of recorded cardiovascular complication was used (see STATISTICAL ANALYSES section).

For multivariate hazard ratio (HR) analyses, simple "yes/no" grouping variables were defined for the following: coronary heart disease (including myocardial infarction and angina pectoris), heart failure, vascular disease of the lower limbs (including clinical and subclinical), and vascular disease of the cerebral vessels (including stroke, reversible and subclinical). Finally, a composite yes/no variable was defined, called "any cardiovascular complication," which included coronary heart disease, heart failure, vascular disease of the lower limbs, and vascular disease of cerebral vessels. It was set at "yes" if at least one value of the four composing variables was "yes."

Table 1—Cardiovascular status at inclusion according to the follow-up over 5 years

	Population *n* = 987	Lost to follow-up *n* = 131 (13.3%)	Died or completed *n* = 856 (86.7%)	*P* (Lost vs. others)	Died *n* = 207 (21.0%)	Completed *n* = 649 (65.8%)	*P* (Died vs. completed)
Coronary heart disease							
Myocardial infarction	211 (21.4)	18 (13.7)	193 (22.5)		54 (26.1)	139 (21.4)	
Angina pectoris	80 (8.1)	13 (9.9)	67 (7.8)		23 (11.1)	44 (6.8)	
No	696 (70.5)	100 (76.3)	596 (69.6)	0.07	130 (62.8)	466 (71.8)	0.029
Heart failure							
Yes	90 (9.1)	10 (7.7)	80 (9.3)		36 (17.4)	44 (6.8)	
No	897 (90.9)	121 (92.4)	776 (90.7)	0.38	171 (82.6)	605 (93.2)	<0.0001
Vascular disease of cerebral vessels							
Stroke	62 (6.3)	9 (6.9)	53 (6.2)		17 (8.2)	36 (5.5)	
Subclinical/reversible	89 (9.0)	15 (11.5)	74 (8.6)		26 (12.6)	48 (7.4)	
Including HSS	45 (4.6)	9 (6.9)	36 (4.2)	0.34	15 (7.2)	21 (3.2)	
No	836 (84.7)	107 (81.7)	729 (85.2)	0.54	164 (79.2)	565 (87.1)	0.0205
Vascular disease of the lower limbs							
Clinical	105 (10.6)	14 (10.7)	91 (10.6)		38 (18.4)	53 (8.2)	
Subclinical	144 (14.6)	14 (10.7)	130 (15.2)		34 (16.4)	96 (14.8)	
Including HSS	55 (5.6)	7 (5.3)	48 (5.6)	0.49	19 (9.2)	29 (4.5)	
No	738 (74.8)	103 (78.6)	635 (74.2)	0.39	135 (65.2)	500 (77.0)	<0.0001
Any cardiovascular complication							
Yes	519 (52.6)	64 (48.9)	455 (53.2)		138 (66.7)	317 (48.8)	
No	468 (47.4)	67 (51.1)	401 (46.8)	0.36	69 (33.3)	332 (51.2)	<0.0001
Amputation							
Yes	20 (2.0)	1 (0.8)	19 (2.2)	0.50	12 (5.8)	7 (1.1)	
No	967 (98.0)	130 (99.2)	837 (97.8)	0.50	195 (94.2)	642 (98.9)	0.0003
Foot wound							
Yes	50 (5.1)	9 (6.9)	41 (4.8)		22 (10.6)	19 (2.9)	
No	937 (94.9)	815 (95.2)	815 (95.2)	0.31	185 (89.4)	630 (97.1)	<0.0001

Values are number (%). HSS, hemodynamic stenosis on sonography.

Statistical Analyses

Values were expressed as medians (interquartile range [IQR]) or percentages. The cumulative value of a quantitative variable was defined for each patient as the mean value over the 5-year follow-up. For qualitative variables, the highest grade of severity observed during follow-up was first obtained for each patient; a yes/no cumulative variable was defined for HR regressions.

Comparisons between groups were performed using the Kruskal-Wallis test and the χ^2 test (Fisher exact test for small samples). Survival was studied using the Kaplan-Meier method, and survival curves were compared with the Breslow-Gehans generalized Wilcoxon test. Multivariate analyses were performed using Cox proportional hazards regression models with stepwise forward and backward procedures. Cumulative variables, as defined previously, were used in these models. SAS 9.4 software (SAS Institute, Inc., Cary, NC) was used for computations.

RESULTS

Patients were 77 years old (median) (IQR 73–80), including 36.7% of patients between the ages of 75 and 80 years and 28.5% of patients aged 80 years and older. They had diabetes for 16 years (10–25). Their BMI was 29 kg/m^2 (26–33), the systolic blood pressure was 140 mmHg (128–150), and the diastolic blood pressure was 73 mmHg (67–80); 90% of the patients were treated with cardiovascular drugs, including diuretics 53%, sartans 40%, ACE inhibitors 39%, β-blockers 38%, calcium channel blockers 37%, nitrates 7%, anticoagulants 12%, and platelet aggregation inhibitors 56%. The HbA_{1c} was 7.3% (6.7–8.1) (56 mmol/mol [50–65]) and the LDL cholesterol was 0.90 g/L (0.70–1.20) (63% of patients were treated with statins). Insulin was used by 58% of the patients and oral antidiabetic drugs by 71%, including metformin in 49%, sulfonylureas in 29%, glinides in 15%, and dipeptidyl peptidase 4 inhibitors in 10% (others <10%). A more detailed description of the population at inclusion can be found in Supplementary Table 1.

During the follow-up, 649 (65.8%) patients completed the study, 207 (21%) died, and 131 (13.3%) were lost to follow-up, including 29 (2.9%) patients who voluntarily stopped the study (Table 1). Among the 207 patients who died during the follow-up, the main recorded cause of death was cardiovascular in 71 (34.3%) patients, including stroke in 19 (9.2%), cerebrovascular involvement in 20 (9.7%), heart failure in 30 (14.5%), mesenteric infarction in 2 (1.0%), and vascular disease of the lower limb in 2 (1.0%). Other causes of death were cancers and malignant hemopathies in 41 patients (19.8%), infections in 25 (12.1%), respiratory insufficiency in 17 (8.2%), renal insufficiency in 14 (6.8%), liver or bowel disease in 10 (4.8%), cachexia in 7 (3.4%), hypoglycemia in 2 (1.0%), and ketoacidosis in 2 (1.0%). The cause of death was not identified in 53 patients (25.6%). Patients lost to follow-up did not differ considerably from the others at baseline; however, many significant differences were found between the patients who died and those who completed the survey (Supplementary Table 1). Cardiovascular complications at inclusion did not differ significantly in the patients lost to follow-up compared with the others (Table 1). They were more frequent among patients who died during follow-up (Table 1). At least one cardiovascular complication was found in about two-thirds of the patients who died during follow-up, versus less than one out of two in those who survived (Table 1).

Progression of Cardiovascular Complications

At 5 years, >40% of the patients had evidence of coronary heart disease (vs. 30% at inclusion), ~20% had heart failure (vs. 9% at inclusion), ~26% had vascular disease of the cerebral vessels (vs. 15% at inclusion), and ~35% had vascular disease of the lower limbs (vs. 25% at inclusion) (Table 2). More than two patients out of three had at least one cardiovascular complication at the end of the study, versus one out of two at inclusion.

Associations Between Cardiovascular Complications and Survival

Patients with coronary heart disease had a significantly lower survival rate than the others, which appeared clearly only in the second half of the follow-up (P = 0.0056) (Supplementary Fig. 1); the association was less strong when patients with infarction and angina pectoris were put into the same group and compared with the group without coronary heart disease (P = 0.019). The outcome was clearly different in patients with or without heart failure ($P < 0.0001$) (Fig. 1); patients with heart failure had poor survival compared with patients without ($P < 0.0001$). A significant, although mild, association was found between survival and vascular disease of the cerebral vessels in two groups (with or without vascular disease of the cerebral vessels: P = 0.026); it was not significant when three groups were considered (with stroke, with subclinical or reversible, or without vascular disease of the cerebral vessels: P = 0.071) (Supplementary Fig. 2). A strong association was found with vascular disease of the lower limbs, both in two (with or without vascular disease of the lower limbs: P = 0.0004) and three groups (with clinical, with subclinical, or without vascular disease of the lower limbs: $P < 0.0001$) (Supplementary Fig. 3). Survival was very different in the small groups of patients with amputation ($P < 0.0001$) (Fig. 2) or with foot wounds ($P < 0.0001$) (Supplementary Fig. 4).

Multivariate HRs

Cardiovascular complications were analyzed simultaneously using the Cox proportional hazards model. In the multivariate model, heart failure was included first (HR 1.96 [95% CI 1.45–2.64], χ^2 = 19.49, $P < 0.0001$), followed by amputation (HR 2.04 [95% CI 1.25–3.35], χ^2 = 8.08, P = 0.0045). It is of note that the model oscillated with another association including heart failure (HR 1.90 [95% CI 1.40–2.57], χ^2 = 17.34, $P < 0.0001$) followed by foot wounds (HR 1.61 [95% CI 1.16–2.24], χ^2 = 8.14, P = 0.0043).

Finally, the yes/no composite variable known as "any cardiovascular complication" (including coronary heart disease, heart failure, vascular disease of the cerebral vessels, and vascular disease of the lower limbs) was included in the model. It appeared only in the third position, after heart failure (HR 1.69 [95% CI 1.23–2.31], χ^2 = 10.51, P = 0.0012) and amputation (HR 1.96 [95% CI 1.20–3.21], χ^2 = 7.17, P = 0.0074), successively, with a slightly significant ratio (HR 1.55 [95% CI 1.08–2.22], χ^2 = 5.67, P = 0.017).

Because many other factors were associated with survival in this cohort (Supplementary Table 1), including individual and geriatric factors, and other complications of diabetes, cardiovascular complications were also studied in a global model. It was developed using all the factors significantly associated with survival (Supplementary Table 1). The model showed five significant variables associated with mortality, successively *1*) institutional living, strongly correlated with geriatric disorders and especially markers of autonomy such as instrumental activities of daily living and activities of daily living scores (HR 2.75 [95% CI 2.04–3.69], χ^2 = 44.90, $P < 0.0001$); *2*) heart failure (HR 1.92 [95% CI 1.43–2.58], χ^2 = 18.88, $P < 0.0001$); *3*) waist-to-hip ratio (HR 1.68 [95% CI 1.26–2.23], χ^2 = 12.45, P = 0.0004); *4*) alcohol consumption (HR 1.58 [95% CI 1.19–2.10], χ^2 = 10.17, P = 0.0014); and *5*) mean HbA_{1c} over 5 years, classified in two classes, <8% and ≥8%, the best cutoff point predictive of death (HR 1.76 [95% CI 1.21–2.57], χ^2 = 8.63, P = 0.0033).

CONCLUSIONS

The main findings of our study dealt with the association between cardiovascular complications and survival in elderly patients with diabetes. All the cardiovascular complications under study were significantly associated with survival, but their associations did not show the same value; heart failure and vascular disease of the lower limbs were very strongly associated with death, whereas coronary heart disease and vascular disease of the cerebral vessels showed only mild associations. This was supported by the multivariate Cox proportional hazards model, which found heart failure as the stronger predictor of death over 5 years. Obvious conclusions should however be considered with caution, because many treatments can be used to improve the progression of coronary heart disease and/or vascular diseases, whereas heart failure is not so easy to improve or prevent. These treatments were likely to have been used in our patients, as 90% of them were treated with cardiovascular drugs at inclusion, 63% with statins, and 7% with fibrates; 12% received anticoagulants and 56% platelet aggregation inhibitors. These drugs could have prevented the occurrence of some complications, mainly those associated with atheroma, and would therefore explain our results (3,4). Another point is that our population is made up of patients aged 70 years and above, and therefore our conclusions cannot be used in younger populations. Similarly, conclusions from studies conducted in younger patients cannot be expected in elderly patients. Clearly, classical risk factors such as hypertension and hypercholesterolemia (3,4,14) were managed in our patients (Supplementary Table 1). This is probably why they did not appear as significant factors of death in our survey.

Among cardiovascular complications of diabetes in our study, heart failure appeared as the most significant predictor of death during follow-up. Furthermore, it remained a significant factor associated with death when all individual, geriatric, and diabetic factors were considered simultaneously (15). This could suggest that heart failure is not only an index of macroangiopathy related to diabetes. Many other mechanisms have been

Diabetes Care Volume 41, January 2018

Table 2—Progression of cumulative values of cardiovascular complications in the 987 patients over 5 years

	Inclusion	1 year	2 years	3 years	4 years	5 years
Coronary heart disease						
Myocardial infarction	211 (21.4)	257 (26.0)	278 (28.2)	293 (29.7)	305 (30.9)	318 (32.2)
Angina pectoris	80 (8.1)	78 (7.9)	81 (8.2)	83 (8.4)	86 (8.7)	88 (8.9)
No	696 (70.5)	652 (66.1)	628 (63.6)	611 (61.9)	596 (60.4)	581 (58.9)
Heart failure						
Yes	90 (9.1)	125 (12.7)	148 (15.0)	163 (16.5)	176 (17.8)	193 (19.5)
No	897 (90.9)	862 (87.3)	839 (85.0)	824 (83.5)	811 (82.2)	794 (80.4)
Vascular disease of cerebral vessels						
Stroke	62 (6.3)	69 (7.0)	75 (7.6)	80 (8.1)	84 (8.5)	91 (9.2)
Subclinical/reversible	89 (9.0)	124 (12.6)	141 (14.3)	151 (15.3)	163 (16.5)	168 (17.0)
Including HSS	45 (4.6)	71 (7.2)	83 (8.4)	94 (9.5)	102 (10.3)	108 (10.9)
No	836 (84.7)	794 (80.4)	771 (78.1)	756 (76.6)	740 (75.0)	728 (73.8)
Vascular disease of the lower limbs						
Clinical	105 (10.6)	116 (11.8)	137 (13.9)	147 (14.9)	155 (15.7)	165 (16.7)
Subclinical	144 (14.6)	160 (16.2)	172 (17.4)	177 (17.9)	180 (18.2)	182 (18.4)
Including HSS	55 (5.6)	71 (7.2)	85 (8.6)	96 (9.7)	102 (10.3)	108 (10.9)
No	738 (74.8)	711 (72.0)	678 (68.7)	663 (67.2)	652 (66.1)	640 (64.8)
Any cardiovascular complication						
Yes	519 (52.6)	579 (58.7)	617 (62.5)	636 (64.4)	651 (66.0)	668 (67.7)
No	468 (47.4)	408 (41.3)	370 (37.5)	351 (35.6)	336 (34.0)	319 (32.3)
Amputation						
Yes	20 (2.0)	29 (2.9)	33 (3.3)	36 (3.6)	38 (3.9)	40 (4.1)
No	967 (98.0)	958 (97.1)	954 (96.7)	951 (96.4)	949 (96.1)	947 (95.9)
Foot wound						
Yes	50 (5.1)	83 (8.4)	111 (11.2)	128 (13.0)	141 (14.3)	153 (15.5)
No	937 (94.9)	904 (91.6)	876 (88.8)	859 (87.0)	846 (85.7)	834 (84.5)

Values are number (%). HSS, hemodynamic stenosis on sonography.

discussed, including microangiopathic, metabolic, hemodynamic, specific diabetic cardiomyopathy, and thrombotic risks, and the influence of autonomic neuropathy on heart failure (16–20). It could therefore be the explanation why heart failure in our study showed the strongest association with death compared with other complications, and even when compared with a composite index of four cardiovascular complications.

Coronary heart disease was the most frequent cardiovascular complication observed in our patients, affecting >40% of them after 5 years. It was strongly associated with poor survival, although less strongly than heart failure. Anyway, our results should not lead to the underestimation of the importance of coronary heart disease in patients with type 2 diabetes and in their outcome.

Consideration should be given to the strong associations observed between poor survival, amputation, and foot wounds. Although they were very strong, these associations concerned only small populations, which is probably why they did not appear in the multivariate analyses.

Another aim of our study was to describe cardiovascular complications and their progression over 5 years in elderly patients with type 2 diabetes, with a median age of 77 years. It showed a large increase in the frequency of cardiovascular complications, from ~50% at inclusion to 67% after 5 years. All complications were involved to various degrees, with the most frequent being coronary heart disease; however, the greatest increase was observed with heart failure (doubled after 5 years). Although approximately half of the patients with diabetes were aged 75 years or above (1,2), the natural progression of cardiovascular complications remains uncertain and has been

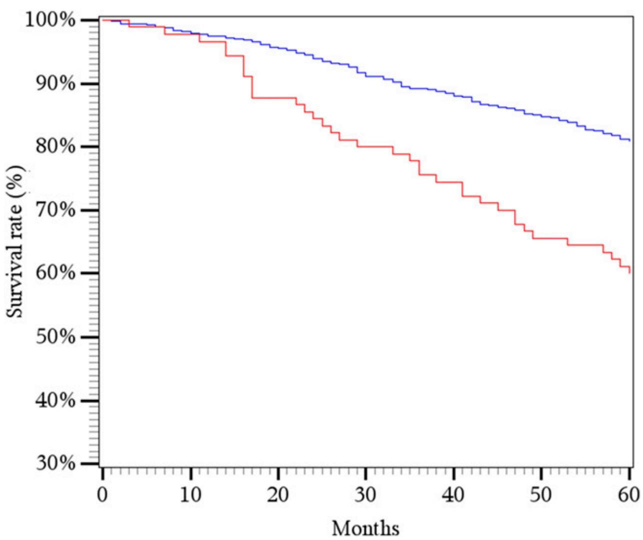

Figure 1—Survival over 5 years in 987 patients with (red line) or without (blue line) heart failure. $P < 0.0001$.

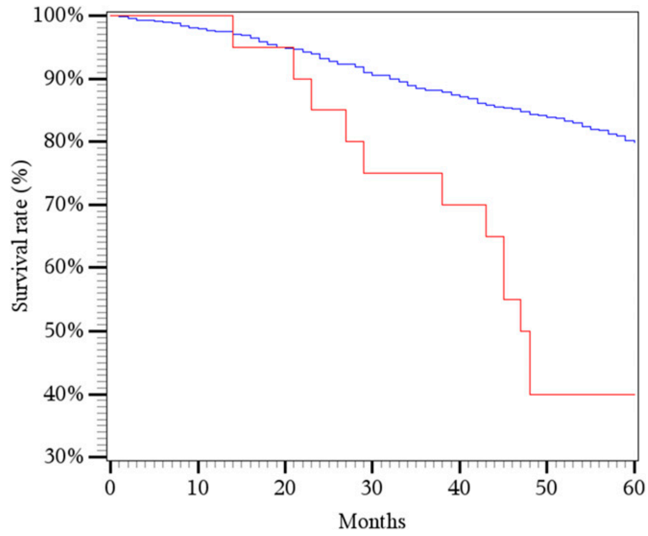

Figure 2—Survival over 5 years in 987 patients with amputation (red line) or without amputation (blue line). $P < 0.0001$.

seldom studied in this age range. This is likely to be related to the recent increase in life expectancy in the general population and to the difficulty managing studies in elderly patients, especially interventional studies (21–23). The different increases in the frequencies of complications have been observed in patients taking several treatments, especially cardiovascular drugs (Supplementary Table 1). The natural progression of the disease itself without the preventive effect of drugs would likely induce more complications. Nevertheless, a large increase in heart failure was observed, although cardiovascular treatments were commonly given to patients (90% at inclusion, increasing to 95% during follow-up). This underlines the influence of diabetes on cardiovascular events despite up-to-date preventive treatment.

Our study is observational and its results should be considered with caution. Consecutive outpatients were recruited, the only specific exclusion criterion being a very low level of autonomy. Many French centers included patients, but they were specialized, and not at the primary level involving GPs. Therefore, some patients could have been overlooked during the recruitment process. However, most patients with diabetes are referred at least once a year to specialized centers by GPs for a standardized checkup. Patients with the most severe forms of diabetes, referred for acute situations, were not included in our study. However, some patients, including those with the less severe forms of diabetes, could be managed only by GPs. In addition, these patients do not necessarily follow the French recommendations. But this recruitment bias is not likely to concern a lot of patients. Therefore, the population under study might be considered a relatively representative sample of elderly French ambulatory patients with diabetes managed according to recommendations, accounting for ~0.1% of the French patients with diabetes in this age range (24).

A limitation of our study is the percentage of patients (13.3%) lost to follow-up. This is not an excessive number compared with previous studies involving younger patients, considering that ambulatory follow-up may be difficult in elderly patients owing to their decreased autonomy or cognitive alterations, or when living far from diabetes centers (21–23). However, the patients lost to follow-up did not differ significantly from the other patients, except for sex and a mildly impaired nutritional status (Supplementary Table 1).

Another limitation concerned the between-centers variability of the diagnosis of the different complications of diabetes, and especially heart failure. It could result from both the variability in the examinations performed and the variability in the classification of the complications in daily life. This could reduce the predictive value of the complications and could bias our results.

Another weakness of the study concerns the associated drugs that were commonly used and not controlled in this study. Many drugs can influence the outcome and could explain our results. On the other hand, our study is a reliable reflection of the true-life evolution in elderly patients with diabetes. Many other causative factors may be involved, including individual characteristics; classical risk factors such as hypertension and dyslipidemia; diabetes characteristics and its other complications, including microangiopathic complications and especially renal failure; and associated diseases and geriatric disorders. Our study tried to consider most of these factors and their influence on survival, especially using Cox models. Multivariate models, although imperfect and limited to studied variables, improved the reliability of our results. They showed the importance of geriatric factors, heart failure, and risk factors such as obesity, alcohol consumption, and glucose control (25,26). Glucose control appears to be a key point in the outcome of patients with diabetes, but the efficiency of intensive treatments remains unclear, mainly because of the hypoglycemic risk (27–29), which is especially high in elderly patients. On the other hand, new drugs without severe risk of hypoglycemic events, which were unavailable or poorly used in our study, could improve the cardiovascular outcome in elderly patients with type 2 diabetes (30,31). Associated treatments are also important to consider and could explain the reasons why some classical risk factors, such as hypertension and hypercholesterolemia, did not appear to be significantly associated with mortality in our model. This does not suggest that they were not important risk factors of mortality in our patients but only that their treatments could be efficient and could reduce this risk. In addition, other important factors might have been overlooked, especially when associated drugs can decrease their effect. As a result, our conclusions should remain cautious, and the negative results should especially not be considered definitive.

In summary, a strong association was found in our study between poor survival in elderly patients with type 2 diabetes and cardiovascular complications, especially heart failure. Interventional studies designed to prevent and/or to improve heart dysfunction should be performed in this population.

Acknowledgments. The authors thank the CRO Umanis (C. Hilbert, J. Fernandes, S. Guerci, and

D. Dubois) for data collection and management. The authors also thank J. Klain-Ratziu of Servon, France, for her contribution to the translation.

Funding. Unrestricted grants were obtained from the French Programme Hospitalier de Recherche Clinique (university grant) and the Francophone Society for Diabetes.

Duality of Interest. Unrestricted grants were provided by Merck Serono and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.B. designed the study, analyzed the results, and wrote and reviewed the manuscript. J.-P.L.F. and J.D. designed the study, analyzed the results, and wrote the manuscript. S.H. wrote and reviewed the manuscript. C.V. designed the study and reviewed the manuscript. J.-P.L.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States [Internet], 2014. Atlanta, Centers for Disease Control and Prevention. Available from www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html. Accessed 1 May 2017

2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14

3. Baena-Díez JM, Peñafiel J, Subirana I, et al.; FRESCO Investigators. Risk of cause-specific death in individuals with diabetes: a competing risk analysis. Diabetes Care 2016;39:1987–1995

4. American Diabetes Association. Cardiovascular disease and risk management. Sec. 9. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S75–S87

5. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359: 1577–1589

6. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Circulation 2009; 119:351–357

7. Mohammedi K, Woodward M, Hirakawa Y, et al.; ADVANCE Collaborative Group. Microvascular and macrovascular disease and risk for major peripheral arterial disease in patients with type 2 diabetes. Diabetes Care 2016;39:1796–1803

8. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664

9. Doucet J, Le Floch JP, Bauduceau B, Verny C; SFD/SFGG Intergroup. GERODIAB: glycaemic control and 5-year morbidity/mortality of type 2 diabetic patients aged 70 years and older: 1. Description of the population at inclusion. Diabetes Metab 2012;38:523–530

10. Bauduceau B, Doucet J, Le Floch JP, Verny C; SFD/SFGG Intergroup and the GERODIAB Group. Cardiovascular events and geriatric scale scores in elderly (70 years old and above) type 2 diabetic patients at inclusion in the GERODIAB cohort. Diabetes Care 2014;37:304–311

11. American Diabetes Association. Older adults. Sec. 11. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S99–S104

12. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–442

13. Haute Autorité de Santé (HAS). National Agency for the Safety of Medicine and Health Products (ANSM). Drug strategy for glycemic control of type 2 diabetes. Recommendations for good practice [Internet]. Available from http://www.has-sante.fr. Accessed 5 January 2013

14. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA 2016;315:1034–1045

15. Bando YK, Murohara T. Diabetes-related heart failure. Circ J 2014;78:576–583

16. Cheung N, Wang JJ, Rogers SL, et al.; ARIC (Atherosclerosis Risk In Communities) Study Investigators. Diabetic retinopathy and risk of heart failure. J Am Coll Cardiol 2008;51:1573–1578

17. Di Bello V, Giorgi D, Pedrinelli R, et al. Coronary microcirculation into different models of left ventricular hypertrophy-hypertensive and athlete's heart: a contrast echocardiographic study. J Hum Hypertens 2003;17:253–263

18. Faden G, Faganello G, De Feo S, et al. The increasing detection of asymptomatic left ventricular dysfunction in patients with type 2 diabetes mellitus without overt cardiac disease: data from the SHORTWAVE study. Diabetes Res Clin Pract 2013;101:309–316

19. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584

20. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). J Am Coll Cardiol 2013;61:447–454

21. Verny C, Doucet J, Bauduceau B, Constans T, Mondon K, Le Floch JP; SFD/SFGG Intergroup. Prevalence of cognitive decline and associated factors in elderly type 2 diabetic patients at inclusion in the GERODIAB cohort. European Geriatric Medicine 2015;6:36–40

22. Gregg EW, Engelgau MM, Narayan V. Complications of diabetes in elderly people. BMJ 2002; 325:916–917

23. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51(Suppl. Guidelines): S265–S280

24. Fagot-Campagna A, Fosse S, Roudier C, et al.; for the ENTRED Scientific Committee. Characteristics, vascular risk and complications in people with diabetes in metropolitan France: significant changes between ENTRED 2001 and ENTRED 2007. Bull Epidemiol Hebd (Paris) 2009;42-43: 450–455 [in French]

25. Palta P, Huang ES, Kalyani RR, Golden SH, Yeh HC. Hemoglobin A1c and mortality in older adults with and without diabetes: results from the National Health and Nutrition Examination Surveys (1988-2011). Diabetes Care 2017;40: 453–460

26. Lang C, Levin D, Mohan M, et al. Effect of glycaemic control on outcome in patients with type 2 diabetes mellitus and chronic heart failure. J Am Coll Cardiol 2015;65(Suppl. 1):A886

27. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358: 2545–2559

28. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358: 2560–2572

29. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139

30. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

31. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375: 311–322