

Development of Congestive Heart Failure in Type 2 Diabetic Patients With Microalbuminuria or Proteinuria

Observations from the DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study

LAURENT VAUR, MD¹
PASCAL GUERET, MD²
MICHEL LIEVRE, PHD³

SYLVIE CHABAUD, PHD³
PHILIPPE PASSA, MD⁴
FOR THE DIABHYCAR STUDY GROUP

OBJECTIVE — The DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study allowed investigators to analyze factors leading to the development of congestive heart failure (CHF) in type 2 diabetic patients with abnormal urinary albumin concentration.

RESEARCH DESIGN AND METHODS — Type 2 diabetic subjects of both sexes aged ≥ 50 years who had a urinary albumin concentration ≥ 20 mg/l were randomly allocated to 1.25 mg/day ramipril or placebo in addition to their usual treatment and treated for 3–6 years in a double-blind fashion. Major outcomes including hospitalization for CHF were recorded during the follow-up.

RESULTS — Of the 4,912 included patients, 187 developed CHF during the study. There was no significant difference in the incidence of CHF between the two treatment groups. Using a multivariate analysis, independent risk factors for the occurrence of CHF were age, history of cardiovascular disease, baseline urinary albumin concentration, baseline HbA_{1c}, and smoking habits. A total of 68 of the 187 patients (36.4%) died during the 12 ± 11 -month period after the first hospitalization for CHF, whereas the annual mortality rate of the population who did not develop CHF was 3.2%.

CONCLUSIONS — Presence of atherosclerotic disease, baseline urinary albumin concentration, and HbA_{1c} level were indicators for further development of CHF. Occurrence of CHF is a major prognostic turn in a diabetic patient's life.

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Epidemiological data indicate a greater risk of congestive heart failure (CHF) in diabetic patients than in nondiabetic patients (1,2). In the Framingham study, the estimated increase in the incidence of CHF for diabetic men and women was twofold and fivefold, respectively (2). The prevalence of diabetes among patients suffering from CHF can be estimated at 20–25% (3) or even more

when the most recent diagnostic criteria for diabetes are used (4). Although increased urinary albumin concentration (UAC) has been recognized as a strong cardiovascular risk factor in diabetic subjects (5), its role in the development of CHF has not yet been investigated (3,6–10). We studied the risk factors for the development of CHF in a large cohort of diabetic patients who were free of symptomatic CHF and had an elevated UAC at baseline. These patients participated in the DIABHYCAR (type 2 DIABETES, Hypertension, Cardiovascular Events and Ramipril) study, a randomized placebo-controlled clinical trial that assessed the effects of a low dose (1.25 mg daily) of the ACE inhibitor ramipril on cardiovascular and renal events in patients with type 2 diabetes and microalbuminuria or proteinuria.

The objective of this article is to describe the characteristics and the prognosis of these diabetic patients developing CHF.

RESEARCH DESIGN AND METHODS

Patients

Type 2 diabetic patients aged ≥ 50 years treated with at least one oral antidiabetic drug and with a UAC ≥ 20 mg/l on two occasions were eligible to enter the study. Patients with a past history of heart failure or with clinical signs or symptoms of CHF at the time of recruitment were excluded. The other main exclusion criteria were treatment with insulin, ACE inhibitor, or angiotensin II receptor antagonist; myocardial infarction within the last 3 months; serum creatinine > 150 $\mu\text{mol/l}$; and any life-threatening disease. All patients had to give written informed consent.

Study design and organization

The design and results of the DIABHYCAR study have been presented in sepa-

From the ¹Medical Department, Aventis, Paris, France; the ²Department of Cardiology, Henri Mondor Hospital, Créteil, France; the ³Department of Clinical Pharmacology, Lyon, France; and the ⁴Department of Diabetology, Saint-Louis Hospital, Paris, France.

Address correspondence and reprint requests to Laurent Vaur, Département Médical, Laboratoires Aventis, 46, Quai de la Rapée, 75012 Paris, France. E-mail: laurent.vaur@aventis.com.

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Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; DIABHYCAR, type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril; LVEF, left ventricular ejection fraction; UAC, urinary albumin concentration.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

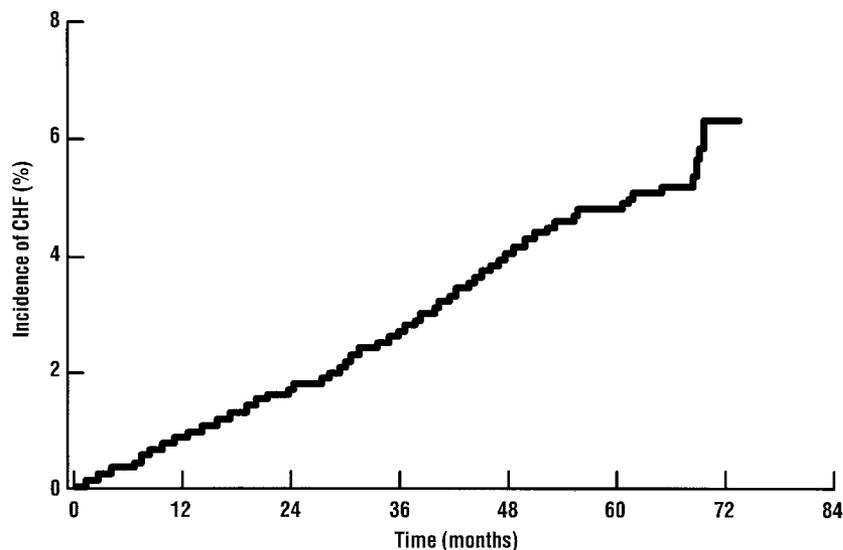


Figure 1—Incidence of newly diagnosed cases of CHF requiring hospitalization during the study.

rate publications (11–13). Study participants are listed in the appendix at the end of this article. The study was conducted mainly by general practitioners. UAC was determined centrally on two occasions 2 months apart before randomization (14). The mean of the two consecutive measurements was used for analysis purposes. At baseline, the following data were collected: age, sex, height, weight, diabetes duration, smoking habits, alcohol consumption, history of hypertension, coronary heart disease (CHD), stroke, and peripheral arterial disease, current treatment, blood pressure, fasting blood glucose, HbA_{1c}, and serum creatinine. HbA_{1c} was measured centrally in France. It was measured locally in other countries, and results were adjusted to those of the French core laboratory, taking into account the normal values for HbA_{1c} in the local laboratories. Patients were followed for 3–6 years after randomization and were seen at 6-month intervals. All cardiovascular and renal events were fully documented by the investigators and, if needed, by direct contact with the hospital in which the patient had been admitted. All the events were then validated by an independent central end point committee with the help of the supporting documentation to ensure that homogeneous diagnoses were made despite the large number of participating investigators.

Definition of heart failure

Both fatal and nonfatal CHF were considered. The diagnosis of CHF required hos-

pitalization and at least two of the following items: 1) clinical signs or symptoms of CHF (pulmonary edema, crepitant rales, gallop rhythm, edema of the lower limbs, hepatomegaly, hepatojugular reflux, or jugular turgescence), 2) typical chest X-ray abnormalities, 3) left ventricular systolic dysfunction, or 4) the

need for treatment with a digitalis, diuretic, ACE inhibitor, and/or inotropic agent. These elements were derived from documents produced by the hospital in which the patient had been admitted. Left ventricular ejection fraction (LVEF) values were collected when available and were determined by the method used in everyday practice by each hospital. Isolated right heart failure was excluded from the definition of CHF.

Statistical methods

Quantitative variables were described by mean \pm 1 SD unless otherwise indicated (median, lower and upper quartiles for variables with non-Gaussian distributions) and were compared by ANOVA. Qualitative variables were described by percentages and compared using Fisher's exact test or Wilcoxon's exact test if appropriate. A multivariate Cox model was used to assess the independent prognostic value of baseline characteristics on the risk of CHF. The following variables were considered prospectively: age, sex, BMI, systolic blood pressure, history of cardiovascular disease (i.e., myocardial infar-

Table 1—Baseline characteristics of patients without and with CHF development during the study

	Patients without CHF	Patients developing CHF	P
n	4,725	187	—
Age (years)	65 \pm 8	69 \pm 8	<0.001
Male sex (%)	70	73	0.417
BMI (kg/m ²)	29 \pm 5	29 \pm 5	0.693
Known duration of diabetes (years) [median (lower, upper quartiles)]	8 (4, 14)	10 (5, 17)	0.0005
Current smokers (%)	18	16	0.594
Drinking >1 alcoholic drink daily (%)	46.3	47.5	0.712
Hypertension (%)	55	67	0.0016
CHD (%)	14	32	<0.001
History of stroke (%)	4	6	0.261
History of peripheral vascular disease (%)	10	23	<0.001
Serum creatinine (μ mol/l)	89 \pm 20	96 \pm 21	<0.001
Fasting blood glucose (mmol/l)	9.8 \pm 3.2	9.8 \pm 3.1	0.926
HbA _{1c} (%)	7.9 \pm 1.8	8.3 \pm 1.9	0.0032
UAC >200 mg/l (%)	25	44	<0.001
UAC (mg/l) [median (lower, upper quartiles)]	74 (37, 206)	155 (48, 493)	0.0001
Systolic blood pressure (mmHg)	145 \pm 15	148 \pm 16	0.045
Diastolic blood pressure (mmHg)	82 \pm 9	82 \pm 8	0.831
Treatment with ramipril (%)	49.9	45.5	0.232

Data are means \pm SD unless otherwise indicated.

tion, angina pectoris, stroke, or peripheral arterial disease), hypertension, smoking >15 cigarettes daily, HbA_{1c}, serum creatinine, UAC, country, and treatment group (ramipril or placebo). In addition, the following parameters were entered in the model if they were found to be predictive of CHF in univariate analyses ($P < 0.05$): antihypertensive treatment, lipid-lowering treatment, antiplatelet treatment, and alcohol consumption (one or more drinks daily). Selection of these variables in the models was done according to the Schwarz criterion, which assesses model fitting, taking into account both the number of parameters and the number of observations (15). A backward procedure was used to keep only variables with a P value < 0.05 . The group of treatment (ramipril or placebo) and country were forced in the final model. Hazard ratios and 95% CIs were used to describe the predictive value of each variable. A Kaplan-Meier survival curve was plotted to describe the incidence of newly diagnosed CHF during the follow-up period.

RESULTS

Patient recruitment

A total of 4,912 patients were recruited between February 1995 and March 1998. There were 3,413 patients recruited in France, 1,200 patients recruited in other European countries (Austria, Belgium, Croatia, the Czech Republic, Germany, Greece, Hungary, the Netherlands, Slovenia, Spain, Switzerland, Turkey, and the U.K.), and 299 patients recruited in North Africa (Morocco and Tunisia).

Incidence of CHF

The mean follow-up was 47 ± 16 months, during which 187 patients were hospitalized for CHF. The incidence of these newly diagnosed cases of CHF is described in Fig. 1. Because the incidence of such events was roughly linear over time, the annual incidence can be estimated at 1.0%.

Predictors of CHF

Table 1 describes patients' baseline characteristics. Patients who developed CHF appeared 4 years older, were more often smokers, and were found more often to have a history of cardiovascular disease; their baseline UAC was higher, as was

Table 2—Factors predicting CHF development: results of the multivariate Cox analysis

	Hazard ratio	95% CI	P
Age (for every 10-year increase)	1.72	(1.68–1.76)	<0.0001
History of cardiovascular disease	2.55	(1.80–3.62)	<0.0001
UAC (for every 10-fold increase in UAC)	2.30	(1.71–3.09)	<0.0001
HbA _{1c} (for every 1% increase)	1.80	(1.08–1.29)	0.0003
Smoking >15 cigarettes daily	1.98	(1.15–3.40)	0.013
Treatment (ramipril vs. placebo)	0.76	(0.54–1.07)	0.120
Germany vs. France	2.00	(0.99–4.04)	0.054
North Europe vs. France	1.54	(0.77–3.07)	0.222
East Europe vs. France	0.66	(0.32–1.39)	0.274
South Europe vs. France	0.18	(0.03–1.29)	0.088
Maghreb vs. France	0.18	(0.03–1.33)	0.093

Treatment group and country were forced in the final model but were not statistically linked to further development of CHF.

their mean HbA_{1c}. In multivariate analysis, these five parameters were predictors of further development of CHF (Table 2). A better fitting was obtained when UAC was entered as log (value) in the model. The model retained neither blood pressure nor being hypertensive at baseline.

Characteristics of diabetic patients with CHF

At the time of hospitalization for CHF, patients were 71 ± 8 years old. Documented CHD was present in 54% of patients, whereas a significant valvulopathy (mainly mitral regurgitation or aortic valve stenosis) was found in 12%. Of the patients, 81% were in New York Heart Association class III or IV. LVEF was determined in 56% of cases and was found below 40% in 51% of patients. Minor dif-

ferences were found between patients with and without CHD (Table 3).

Prognosis

A total of 658 of the 4,912 randomized patients (13.4%) died during the follow-up. There were 590 deaths among the 4,725 patients who did not develop CHF during the study, with a mean follow-up of 47 ± 16 months corresponding to a 3.2% annual mortality.

One-year mortality was nearly 12 times higher (36.4%) in patients who developed CHF during the study, with 68 of 187 patients dying an average of 12 + 11 months after the first hospital admission for CHF. There were 38 deaths in CHD patients who developed CHF (37.6%) and 30 deaths in non-CHD patients who developed CHF (34.8%).

Table 3—Characteristics of patients developing CHF during the study at the time of diagnosis of CHF

	Missing data (%)	Patients with CHD	Patients without CHD	P
n		101	86	
Age (years)	0	71 ± 8	72 ± 8	0.52
Male sex (%)	0	77	67	0.14
Treated hypertension or blood pressure >140/90 mmHg at two visits (%)	0	59	74	0.043
Prior myocardial infarction (%)	0	53	0	Not relevant
Significant valvulopathy (%)	0	13	10	0.66
NYHA functional class (%) (I/II/III/IV)	22	3/14/26/57	1/21/37/41	0.089
LVEF <40% (%)	44	61	37	0.018
Chronic or paroxysmal atrial fibrillation (%)	0	28	36	0.27

NYHA, New York Heart Association.

CONCLUSIONS

Incidence of CHF in diabetic patients

Published estimates of incident CHF in type 2 diabetes range from 3 to 33 cases per 1,000 patient-years (1,2,16–18). Apart from the U.K. Prospective Diabetes Study (UKPDS), almost all studies that could estimate incidence of CHF in diabetes were performed in the U.S. in unselected diabetic patients. The DIABHYCAR study gave us the opportunity to evaluate such incidence in a European selected population of albuminuric type 2 diabetic patients. We found that the annual incidence of CHF was 10 cases for 1,000 patients. However, this figure must be interpreted cautiously. By excluding cases of CHF that did not require hospitalization, we neglected less severe cases of CHF and underestimated the overall incidence of CHF. We may have overestimated the number of patients hospitalized for CHF because some patients admitted to the hospital for other reasons than CHF may have been finally considered by the central end point committee as having a diagnosis of CHF. In addition, this incidence rate was derived from a selected population and cannot be extrapolated to the general population of type 2 diabetic patients: on the one hand, the need for an age >50 years and a high UAC at inclusion increased the risk of the population; on the other hand, the selection process for a clinical trial generally favors the recruitment of healthier patients. Specific exclusion criteria such as treatment with insulin or renin-angiotensin system inhibitors likely determined lower-risk patients.

Etiology

Heart failure is the common end of many different disease processes that impair cardiac function. CHD accounts for half the cases of CHF overall as well as in the subgroup of diabetic patients (18,19). Isolated silent myocardial ischemia may lead to CHF and interacts with diabetes to accelerate the progression of myocardial dysfunction (20). Valvular heart disease is now an infrequent underlying etiology in the developed world, representing <5% of cases. When causes are regarded as mutually exclusive, hypertension alone also represents a rare etiology (21). In the rest of cases, the etiology (19) is unknown and the term “primary cardiomyopathy” is ap-

plied. Independent left ventricular dysfunction associated with diabetes alone has sometimes been termed “diabetic cardiomyopathy” (22,23). It is characterized initially by diastolic dysfunction with reduced early diastolic filling and increased left ventricular wall thickness and is followed some years later by systolic dysfunction (24). In our study, more than half the patients who developed CHF had CHD, whereas significant valvulopathies were rare. The subgroup of CHF patients without CHD probably comprised a vast majority of diabetic cardiomyopathies. In this subgroup, there was a high percentage of patients with LVEF \geq 40%. This percentage was probably underestimated because missing data were more likely for patients with preserved LVEF. This finding may confirm the later development of systolic dysfunction in primary diabetic cardiomyopathy.

UAC and the development of CHF

Microalbuminuria has been recognized as a powerful and independent marker of vascular risk in diabetes (5). Several survival studies conducted in type 2 diabetic patients have shown that microalbuminuria is associated with a two- to threefold increased risk of all-cause and cardiovascular mortality (25,26). Microalbuminuria has also been determined a risk factor for incident CHD, at least in men (27,28). In our study, we found a correlation between level of UAC and further development of CHF in patients with elevated UAC at baseline. The relationship was found to be logarithmic, with each 10-fold increase in baseline UAC associated with a more than doubled risk of CHF. This finding might just confirm the link between high UAC and further development of vascular disease. Alternatively, higher baseline UAC could be a consequence of renal venous congestion, the latter being an early manifestation of pre-clinical CHF.

Blood glucose control, blood pressure control, and the development of CHF

Several studies have suggested an independent, graded association between glycemic control and the incidence of hospitalization due to CHF among diabetic patients (29–31). In a cohort of almost 50,000 diabetic subjects, Iribarren et al. (29) demonstrated that each 1% increase in baseline HbA_{1c} was associated

with an 8% increased risk of CHF, after adjustment for confounding factors. In the UKPDS, each 1% increase in updated mean HbA_{1c} was associated with a 19% increase in risk of nonfatal CHF (30). However, there was no association between baseline HbA_{1c} and the risk of CHF in the UKPDS. In the present study, each 1% increase in baseline HbA_{1c} was associated with an 18% increased risk of CHF. The lack of association of baseline HbA_{1c} with CHF in the UKPDS may be because UKPDS patients were included with newly diagnosed diabetes, whereas in the DIABHYCAR study, on average, patients were included after 8 years of diabetes. When baseline HbA_{1c} was corrected by values recorded during follow-up in the UKPDS (updated HbA_{1c}), a significant association was found with CHF, as in the DIABHYCAR study. These results suggest that improved long-term glycemic control may reduce the risk of developing CHF.

Despite a marginally significant higher baseline systolic blood pressure in patients developing CHF, we did not find any link between baseline blood pressure and further incidence of CHF in the multivariate analysis. This fails to confirm the findings of the UKPDS, where each 10-mmHg increase in updated mean systolic blood pressure was associated with a 14% increase in risk of CHF (32). These results were consistent with those achieved by the policy of tight blood pressure control in the UKPDS clinical trial. The lack of link in our study might be due to inaccurate measurement of blood pressure at baseline (only one casual measurement with a nonautomatic device) or to the inclusion of patients with a narrow range of well-controlled blood pressures. Alternatively, because this study included only patients with elevated UAC, it is possible that such a link would have become less apparent: indeed, most damages due to elevated blood pressure might occur earlier, before the appearance of albuminuria.

Prognosis

Information on the prognosis of CHF can be derived from population-based studies, hospital series, or intervention trials. In population-based studies such as the Framingham Heart Study or the Minnesota study, mortality 1 year after diagnosis of CHF was 34%, with the median survival being 1.7 years in women and 3.2 years in men (33,34). Hospital series tend

to reflect the patient population of specialist referral centers and thus often include the most severe cases. In these reports, mortality 1 year after the first hospitalization for CHF ranged from 21 to 48% (35–37). Pharmacological trials include highly selected patients who are usually at a lower risk of outcome than the targeted population. Mortality 1 year after inclusion in the control arms of clinical trials for CHF varied from 11 to 52% (38–41). When the information was available, there was no evidence in these studies for an increased risk of death from CHF in diabetic patients compared with nondiabetic patients. The 1-year mortality rate of 36% found in our study is in line with these previous results and confirms the poor prognosis of diabetic patients developing heart failure; it also tends to show that France shares with the U.S. and Scandinavia the same unfavorable prognosis for these patients.

In conclusion, the DIABHYCAR study data confirm the high frequency and poor prognosis of CHF in type 2 diabetes. It underlines that in diabetic patients with elevated UAC, the higher the UAC level, the higher the risk of later developing CHF. These data warrant a re-evaluation of strategies for preventing and treating heart failure in the rapidly growing population of elderly type 2 diabetic patients.

APPENDIX: STUDY PARTICIPANTS

Principal Investigator: Prof. M. Marre (Bichat Hospital, Paris, France); *National Coordinators:* Austria: G. Schernthaner; Belgium: R. Rottiers; Croatia: V. Profozic; Czech Republic: J. Perusicova; France: M. Marre; Germany: J. Mann; Greece: S. Pappas; Hungary: G. Pogatsa; Morocco: J. Belkhadir and F. Hakkou; the Netherlands: J. Jonker; Slovenia: G. Schernthaner; Spain: F. Hawkins; Switzerland: K. Scheidegger; Tunisia: M. Gueddiche; Turkey: U. Gorpe; U.K.: G.C. Viberti; *Steering Committee:* F. Alhenc-Gelas, J.P. Boissel, F. Cambien, S. Etienne, A. Girault-Louvel, P. Gueret, M. Lièvre, J. Mann (Vice-Chairman), M. Marre, J. Ménard, P. Passa (Chairman), P.F. Plouin, D. Vasmant, L. Vaur (Secretary), G.C. Viberti, and C. Weisselberg; *Central Coordinating Center:* J.P. Boissel and M. Lièvre; *Executive Committee:* J.P. Boissel, V. Bost, M. Cambien, Y. Gallois, N. Genes, J. Gil-

let, M. Hervé, M. Lièvre, M. Marre, L. Martin, A. Perret-Hantzperg, P.F. Plouin, and L. Vaur; *Biological Committee:* F. Alhenc-Gelas (Chairman), F. Cambien, A. Girault-Louvel (Vice-Chairman), M. Lièvre, M. Marre, and J. Ménard; *Central End Point Committee:* E. Bonnefoy, G. Chatellier (Chairman), T. Moreau, and L. Pinède; *Independent Data and Safety Committee:* E. Eschwege, C.E. Mogensen, N. Victor, and S. Weber.

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