Impact of diabetes on the current in-hospital management of heart failure. From the TEMISTOCLE study

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Key words:
Diabetes mellitus; Heart failure.

Background. **Little is known about the clinical profile, use of resources, management and outcome of a large population of diabetic patients with heart failure managed in a community setting.**

Methods. **A prospective cross-sectional survey in the setting of acute hospital admissions for heart failure to 167 cardiology and 250 internal medicine departments between February 14 and 25, 2000.**

Results. **Among the 2127 consecutively admitted patients, 603 (28.4%) had a history of diabetes; they were significantly younger, had a lower rate of atrial fibrillation, and a more frequent ischemic etiology than non-diabetics. Just as non-diabetic patients, diabetics underwent invasive and non-invasive procedures in a low percentage of cases, even though slightly more frequently when managed by cardiologists. Diabetic patients were less frequently prescribed amiodarone and anticoagulants, and more frequently prescribed nitrates and antiplatelets. The all-cause in-hospital mortality rate was similar among diabetics and non-diabetics (5.3 vs 5.7%, p = NS). Adjusted analysis confirmed that diabetes is not independently associated with a worse outcome.**

Conclusions. **In a community setting diabetes *per se* has only a slight impact on the management and outcome of patients with heart failure.**

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Introduction

Cardiac patients with diabetes mellitus are identified, in general, as a cohort with a poorer outcome, a higher rate of complications and a greater impact on health care resources. For instance, they have less favorable acute and long-term outcomes after myocardial infarction[1-6] or after cardiac procedures such as balloon angioplasty, stent implantation[1-10] or revascularization via coronary artery bypass grafting[11-13].

Diabetes mellitus affects approximately 15 to 35% of patients with chronic heart failure (HF) in the community setting and in trials[14-31], and is emerging as a negative prognostic factor for morbidity and mortality even in asymptomatic patients with a left ventricular ejection fraction ≤ 45%[25,32-35]. Further, poor glycemic control could accelerate the progression[36] and precipitate destabilization of HF[37].

The most appropriate management of diabetic subjects has still not been determined[38]. Subgroup analyses of randomized clinical trials show that diabetic and non-diabetic patients derive equal benefit from HF pharmacological treatment such as ACE-inhibitors[28,32,39] or beta-blockers[25,35,40]. Little is known about the current management of diabetic patients with HF, which should not be limited to patients cared for by cardiologists but which should also be employed for those cared for by internists[41-43], who generally have more frequent comorbidities.

To evaluate the impact of diabetes on the HF management of a consecutive cohort of patients hospitalized for worsening HF, we compared the in-hospital clinical profile, use of resources, treatment and 6-month outcome between non-diabetic and diabetic patients enrolled in the TEMISTOCLE study (hearT failurE epideMIological STudy fadOi-anmCo in itaLian pEople). A similar comparison was made within the diabetic group, between patients admitted to cardiology (CARD) or internal medicine departments (MED) in relation to some health management aspects.

Methods

Details of the TEMISTOCLE study have been previously described[44]. In brief, the TEMISTOCLE survey was a prospective cross-sectional survey conducted in a network of 167 CARD units and 250 MED units. The study was endorsed by the Italian Association of Hospital Cardiologists (ANMCO) and the Italian Federation of Hospital Internists (FADOI). The TEMISTOCLE survey had the aim of identifying the differences in the clinical profile, use of resources, management and outcome of a large population of patients admitted for HF. It prospectively evaluated all patients with a primary discharge diagnosis of HF made according to the criteria of the European Society of Cardiology guidelines[45], admitted to the 417 participating centers between February 14 and 25, 2000.

Data about the patients' history, physical examination, diagnostic procedures and in-hospital course were recorded at discharge on a standardized form to allow assessment of provider-related differences in the clinical profile of the study population. Potential differences in the patients' management were assessed by comparing the frequency of diagnostic tests at hospital admission, pharmacological treatment during hospital stay and at discharge and patients' referral for follow-up. Comorbidity was defined as the presence of at least one of the following: chronic obstructive pulmonary disease, renal dysfunction, anemia, and thyroid disease. The diagnosis of diabetes mellitus was based on the patient's self-report or on documentation in his/her medical records. In all cases the diagnosis was biochemically confirmed during hospitalization.

The evaluation of the in-hospital outcome included the length of hospital stay, New York Heart Association (NYHA) functional class at discharge and all-cause in-hospital mortality. Follow-up visits were not formally requested by the study protocol and were performed in accordance with the routine clinical practice of the participating centers.

Statistical analysis. Data were sent to the ANMCO Research Center, where they were checked for accuracy and completeness. The study cohort was stratified according to the presence or absence of diabetes and, in diabetic patients, according to their admission to either a CARD or a MED unit.

Continuous variables were expressed as mean ± SD. Differences between continuous variables were evaluated using the Student's t-test. Discrete variables were summarized by frequency percent and compared using χ^2 tests. A multivariate logistic regression analysis was used in order to evaluate the independent predictors of all-cause in-hospital mortality. The results are expressed as odds ratios with 95% confidence intervals. A p value < 0.05 was considered as statistically significant.

Results

Patient population. Between February 14 and 25, 2000, the 417 participating centers enrolled 2127 consecutive patients admitted for HF. CARD units (n = 167, 40.1% of total centers) enrolled 789 patients (37.1% of total cases), while 1338 patients (62.9%) were enlisted in 250 MED units (59.9% of centers). Of these patients, 603 (28.4%) were diabetics and were enrolled in similar percentages in the CARD and MED units (27.1 vs 29.1%, p = NS). Most admissions in both groups were urgent, but significantly more in diabetic patients (93.0 vs 89.7%, p = 0.00172). The baseline demographic and clinical features of the enrolled patients are summarized in table I. Diabetic patients were significantly younger, more frequently female and had a similar degree of left ventricular systolic dysfunction. Atrial flutter-fibrillation was very frequent in both groups but significantly less prevalent in diabetic patients.

In-hospital course. The length of stay, and diagnostic and therapeutic procedures performed during hospitalization are described in table II. Diabetes *per se* did not affect the length of hospital stay, although the diabetic patients admitted to MED wards stayed in hospital significantly longer than those admitted to CARD units. Moreover, a history of diabetes did not influence the use of diagnostic tests (non-invasive or invasive procedures), whose absolute numbers were rather low even among patients admitted into CARD Units. Left ventricular dysfunction was detected in 58.0% of diabetic patients (55.2% in non-diabetic patients, p = NS), in almost all cases (96.8%) at echocardiography and more frequently in CARD units (82.2 vs 44.7%, $p < 0.0001$). Among cardiovascular procedures, independently of the metabolic comorbidity, CARD diabetic patients more frequently underwent electrical antiarrhythmic therapy during hospitalization than MED ones (Table II). Table III shows the prescription patterns during hospitalization and at discharge. Of note, amiodarone and anticoagulants were significantly less frequently prescribed in diabetic patients, while nitrates and antiplatelets were significantly more frequently prescribed in these patients. Other slight differences in vasodilator, calcium antagonist and statin use were present only during hospitalization. Anticoagulants were considered as being not indicated in a greater number of diabetic patients (54.5 vs 47.6%, p = 0.0132), while old age was the reason for non-prescription more frequently in non-diabetic (28.6 vs 18.9%, $p < 0.0001$) than in diabetic patients. The prescription of ACE-inhibitors and/or angiotensin-receptor blockers was similar in the two types of units (MED 78% vs CARD 73%, p = NS). Beta-blockers were infrequently prescribed (MED 8% vs CARD 14%, p = 0.0278). Table IV shows the main reasons put forward by the attending physicians for the non-prescription of beta-blockers

Table I. Clinical characteristics of diabetic versus non-diabetic patients at enrolment.

	All cases (n=2127)	Diabetics (n=603)	Non-diabetics (n=1524)	p
Age (years)	74 ± 12	73 ± 10	75 ± 12	0.0006
≥ 75 years (%)	52.1	44.9	55.0	< 0.0001
Female gender (%)	47.0	50.9	45.4	0.02
Hospital admissions (in the previous year) (%)	43.5	43.4	43.6	NS
Symptom duration ≤ 12 months (%)	58.7	57.3	59.2	NS
Symptom severity (%)				
NYHA classes I-II-III	44.2	43.0	44.7	NS
NYHA class IV	31.2	30.5	31.4	
Pulmonary edema	22.2	24.2	21.5	
Cardiogenic shock	2.4	2.3	2.4	
Atrial flutter-fibrillation (%)	44.7	39.3	46.8	0.0075
Etiology (%)				< 0.0001
Ischemic	41.8	50.2	38.5	
Hypertensive	22.2	23.4	21.7	
Dilated cardiomyopathy	10.6	10.8	10.5	
Valvular	14.4	8.1	16.9	
Other	5.3	3.3	6.1	
Not known	5.7	4.2	6.3	
Measured LVEF	1182 (55.6%)	350 (58.0%)	840 (55.2%)	NS
< 30%	27.3	24.3	28.6	NS
30-40%	38.5	39.0	38.3	
> 40%	34.2	36.7	33.1	
Comorbidity* (%)	57.2	54.2	58.5	NS
COPD	41.3	38.6	42.3	NS
Renal dysfunction (creatinine > 2.5 mg/dl)	8.4	7.6	8.7	NS
Anemia	13.9	14.4	13.7	NS
Thyroid disease	6.4	5.8	6.6	NS

COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction. * diabetes excluded.

Table II. Diagnostic and therapeutic procedures during hospital stay.

	All cases (n=2127)	Diabetics (n=603)	Non-diabetics (n=1524)	p	Diabetics		
					Medicine (n=389)	Cardiology (n=214)	p
Length of hospital stay (days)	11.2 ± 7.7	11.7 ± 7.7	11.8 ± 7.4	NS	12 ± 8	10 ± 6	0.0018
In-hospital mortality (%)	5.6	5.3	5.7	NS	5.8	6.0	NS
Diagnostic evaluation (%)							
Echocardiography	67.6	69.4	66.8	NS	57.0	92.0	< 0.0001
Holter monitoring	15.8	14.2	16.4	NS	7.2	27.1	< 0.0001
Exercise test	2.4	1.6	2.6	NS	0.7	3.2	0.0391
Stress testing*	4.0	3.3	4.3	NS	1.3	7.0	0.0002
Right ventricular catheterization**	3.4	2.5	3.7	NS	1.8	3.7	NS
Coronary angiography	3.3	3.7	3.2	NS	1.0	8.4	< 0.0001
Thoracic CT scan	1.9	1.16	2.2	NS	1.0	1.4	NS
Cardiovascular procedures (%)							
Pacemaker implantation (temporary or definitive)	2.0	2.0	2.0	NS	0.8	4.2	0.0039
AICD implantation	0	0	0	NS	0	0	NS
Electrical conversion from atrial F-F	1.41	1.16	1.51	NS	0.26	2.8	0.0052
Percutaneous coronary intervention	0.1	0.33	0	NS	0.2	0.4	NS
Coronary artery bypass grafting	0.2	0.5	0	NS	0.5	0	0.0192

AICD = automated implanted cardioverter-defibrillator; CT = computed tomography; F-F = flutter-fibrillation. * exercise test or stress echo or myocardial scintigraphy; ** monitoring or testing.

in both diabetic and non-diabetic patients. Only peripheral vasculopathy was indicated more frequently in diabetics, while chronic obstructive pulmonary disease and older age were the more frequent factors for non-prescription in non-diabetic patients. Diabetes *per se* was considered a contraindication to beta-blockers in

Table III. Medical treatment during hospital stay and at discharge in diabetic and non-diabetic patients.

	In-hospital (%)			At discharge (%)		
	Diabetics (n=603)	Non-diabetics (n=1524)	p	Diabetics (n=571)	Non-diabetics (n=1436)	p
Inotropes	17.6	18.8	NS	4.4	5.9	NS
ACE-inhibitors	75.0	70.9	NS	75.8	73.3	NS
Digoxin	66.7	68.6	NS	58.8	61.7	NS
Furosemide	96.2	95.3	NS	87.7	86.7	NS
Spironolactone	40.5	41.2	NS	38.0	37.9	NS
Beta-blockers	9.1	11.0	NS	10.2	12.8	NS
Angiotensin receptor blockers	7.3	6.4	NS	7.2	7.4	NS
Amiodarone	13.1	17.6	0.0117	10.5	14.8	0.0108
Other antiarrhythmics	3.1	2.8	NS	1.2	2.0	NS
Nitrates	59.2	48.6	< 0.0001	52.9	42.6	< 0.0001
Other vasodilators	5.8	3.7	0.0349	4.9	3.4	NS
Calcium channel blockers	19.2	15.5	0.0395	17.5	14.5	NS
Statins	6.8	4.7	0.0464	7.0	5.1	NS
Oral anticoagulants	24.4	29.5	0.0186	19.4	26.0	0.0018
Antiplatelet agents	45.1	36.5	0.0002	46.2	37.9	0.0006

Table IV. Reasons for not prescribing beta-blocker treatment in patients with and without diabetes.

	Diabetics (%)	Non-diabetics (%)	p
Bradyarrhythmias	4.1	3.5	NS
Hypotension	6.4	7.4	NS
NYHA class IV	13.3	14	NS
Peripheral vasculopathy	2.5	0.9	0.0110
COPD	35.4	40.7	0.0400
Old age	36.5	29	0.0025

COPD = chronic obstructive pulmonary disease.

less than a quarter of the diabetic patients (MED 24.1% vs CARD 12.7%, p = 0.0024).

Precipitating factors. The factors which were considered as having potentially worsened HF are shown in table V. In diabetics, these were more frequently myocardial ischemia and other factors which were somehow related to the metabolic disorder.

Clinical outcome. Diabetes *per se* did not affect the all-cause in-hospital mortality, as shown in table VI in which the variables related to mortality are listed. During the hospital stay 32 diabetic patients died. No differences were observed in mortality between MED and CARD patients (4.8 vs 6.1%, p = NS) even after adjusted analysis. Worsening HF was the main cause of death in both groups (78.1% in diabetic vs 78.4% in non-diabetic patients, p = NS). At discharge, only 22% of diabetic patients were in NYHA class III-IV while atrial fibrillation was still present in 29.4%. The planned management at discharge did not differ among diabetic and non-diabetic patients (Table VII). A 6-month follow-up visit was performed only in 323 diabetic and 809 non-diabetic patients (56.6 vs 56.3%).

Table V. Precipitating factors.

	Diabetics (n=603)	Non-diabetics (n=1524)	p
Not identified	9.3	12.4	NS
Myocardial ischemia	29.2	22.8	0.0031
Uncontrolled hypertension	23.6	20.2	NS
Arrhythmias	19.6	23.8	0.0448
Pulmonary disease	39.8	41.0	NS
Endocrine dysfunction*	34.9	4.3	< 0.0001
Hyperthyroidism	2.2	2.7	
Uncontrolled diabetes	28.8	–	
Other	0.6	1.0	
Anemia	12.6	12.0	NS
Infectious disease	14.3	11.9	NS
Iatrogenic factors**	20.3	17.3	NS
Dietary factors***	10.8	4.9	< 0.0001

Values are expressed as percentage. More than one factor could be attributed to the same patient. * endocrine dysfunction is comprehensive of diabetes and other endocrine factors; ** iatrogenic factors are comprehensive of poor drug compliance and inappropriate drug prescription; *** dietary factors include inappropriate use of alcohol, liquids and salt.

Table VI. Multivariate analysis of all-cause in-hospital mortality.

	OR	95% CI
Age (years)	1.05	1.03-1.08
LVEF available (no vs yes)	1.85	1.17-2.92
Ischemic vs non-ischemic etiology	1.57	1.01-2.42
Unknown vs non-ischemic etiology	3.64	1.90-6.99
Creatinine > 2.5 vs ≤ 2.5 mg/dl	3.14	1.88-5.25
Shock/pulmonary edema/NYHA IV vs NYHA I-II-III	5.36	3.00-9.58
ACE-inhibitors (yes vs no)	0.61	0.41-0.93
Spironolactone (yes vs no)	1.51	1.00-2.29
Diabetes	1.12	0.72-1.76

CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio.

Table VII. Planning at discharge and 6-month follow-up data.

	Diabetics (n=571)	Non-diabetics (n=1436)	p	Diabetics		
				Medicine (n=370)	Cardiology (n=201)	p
Planning at discharge (%)						
Discharged home	94.0	93.0	NS	93.5	95.0	NS
Follow-up instrumental evaluation	8.9	11.2	NS	7.8	10.9	NS
Follow-up outpatient clinic	81.3	80.0	NS	78.1	87.1	0.0088
6-month follow-up (%)						
6-month visit performed	56.6	56.3	NS	50.5	67.6	0.0001

Discussion

The prevalence of a history of diabetes mellitus in this large series of unselected patients admitted for worsening HF into CARD or MED units was 28%, similar to that reported in previous studies[14-18,20-23,25,26,28,29,31]. In this respect, no differences emerged between patients with HF recruited mainly by CARD units in controlled trials and those admitted in non-specialist wards.

In our survey, diabetic patients with HF differed from those without this disorder. Diabetics were slightly younger, more often female, and more frequently had a history of coronary artery disease which was present in at least half of them. Thus, diabetes confirmed its contribution to the acceleration of the remodeling processes which could anticipate the development of HF in diabetics. Some hypotheses relative to this increased susceptibility to HF, already known from the Framingham study[46], have been suggested. These include a different distribution and severity of coronary disease, the recurrence of silent ischemic episodes, as well as myocyte hypertrophy and necrosis, interstitial fibrosis, intramyocardial microangiopathy, endothelial factors, autonomic tone or cardiac metabolic dysfunctions[47-49].

In this population of relatively elderly patients, coming from the "real world" practice, the distribution of left ventricular dysfunction was similar between diabetic and non-diabetic patients, the prevalence of a preserved left ventricular function being around 34%.

Interestingly, renal dysfunction was equally frequent in diabetic and non-diabetic patients.

The proportion of patients who underwent diagnostic or therapeutic procedures during hospitalization was very low in all patients and in both settings, with the notable exception of echocardiography, without any difference related to diabetes. Diabetic patients underwent coronary angiography in 3.7% of the cases. This rate is surprisingly low considering that diabetic patients are relatively young and that the etiology of HF is prevalently ischemic.

Diabetes seems to only slightly affect therapeutic choices. Amiodarone and anticoagulants were less frequently prescribed (in part related to the lower prevalence of atrial fibrillation at entry), while anti-ischemic drugs as well as antiplatelets were more frequently prescribed in diabetic patients (in part related to the higher rate of ischemic disease). Beta-blockers were still used in only a low percentage of patients in both groups (possibly due to the fact that the population of this study consisted of elderly, frail and unstable patients). Despite the fact that subgroup analyses of trials have shown similar positive results in both diabetic and non-diabetic patients[25,35,40], diabetes *per se* is still perceived as a reason for not prescribing beta-blockers in about a quarter of diabetic patients, particularly by internists who presumably fear the induction of a lower sensitivity to hypoglycemia. A further reason for prescribing these drugs less frequently in diabetics is the presence of peripheral vasculopathy, a frequent complication of this disease. Finally, current guidelines suggest the use of beta-blockers in hemodynamically stable patients, while the population of this survey mainly consisted of patients who had a recent destabilization which led to hospital admission.

Of note, ACE-inhibitors were widely used in diabetic and non-diabetic patients by both cardiologists and internists. This treatment, shown to be useful in diabetic patients[16,17,28,50,51], may be considered as being well implemented in current practice.

The causes of worsening HF leading to hospital admission were different in diabetic and non-diabetic patients. Myocardial ischemia together with non-compliance to the prescribed diet were reported as more frequent in diabetic than in non-diabetic patients. Uncontrolled diabetes was frequently associated with episodes of HF destabilization, maybe as a consequence of tachycardia, thirst, excessive osmotic diuresis, and dehydration.

Interestingly, diabetes did not cause a longer period of in-hospital stay. Moreover, multivariate analysis, adjusted for the most relevant clinical variables including age, showed that the all-cause in-hospital mortality was independent of the provider and similar in diabetic and non-diabetic patients. It should be stressed that the all-cause in-hospital mortality, mainly due to HF, was lower than previously reported[52,53] suggesting a possible improvement in therapeutic regimens.

With respect to the outcome, the data derived from *post-hoc* analyses of several trials suggest that diabetes is *per se* a negative prognostic factor in terms of the 6-month mortality and re-hospitalization rates. For instance, the SOLVD studies[32,34] found that ischemic diabetic patients had a poorer outcome than non-diabetic and non-ischemic diabetic patients, suggesting a different impact of diabetes on the prognosis according to the etiology. Suskin et al.[33] from the RESOLVD trial found that diabetic patients more frequently experienced clinical events than non-diabetic patients during a 43-week follow-up. In Suskin's study, 13.6% of the diabetic patients were hospitalized due to worsening HF compared to 8.6% of non-diabetic patients ($p = 0.057$). Finally, in the BRING-UP study, the 1-year all-cause mortality and hospitalization rates were higher for diabetic patients than for non-diabetics (15.8 vs 10.9%, $p = 0.001$)[54].

Follow-up visits were not a mandatory procedure in the TEMISTOCLE study; consequently, its relatively low rate, which may mirror everyday CARD as well as MED clinical practice, precludes a reliable comparison of these data with those of *post-hoc* analyses of clinical trials and suggests that a further effort should be made to increase knowledge regarding structured follow-up procedures.

Study limitations. The TEMISTOCLE survey might have been biased due to the centers interested in participating: some CARD centers might have been specialized or interested in HF, while participating MED departments were probably only cardiology-oriented. Secondly, follow-up visits were not a mandatory procedure in the study. Finally, the TEMISTOCLE survey did not have a pre-specified interest in the impact of diabetes on the management of HF; thus, some variables such as the type of diabetes, duration and severity of disease, metabolic control (i.e. glycosylated hemoglobin) and metabolic drugs were not specifically reported in the case report forms.

In conclusion, studies such as TEMISTOCLE and other community series[53,55,56], allow us to move from the "typical trial patient" to the "typical real world patient".

Further knowledge is needed about the pathophysiology of HF in patients with diabetes. Furthermore, there still is uncertainty regarding the most effective pharmacological strategy to be used in diabetic patients with HF. On the basis of our survey we can conclude that, in clinical practice, cardiologists and internists manage both diabetics and non-diabetics in the same way.

Appendix

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