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ORIGINAL ARTICLE

Age affects the prognostic impact of diabetes in chronic heart failure

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Abstract

Aims Increasing age is an established prognostic determinant in chronic heart failure (HF). Diabetes often complicates HF in its course and appears to worsen HF prognosis. A differential impact of diabetes depending on patients' age was not yet studied. We evaluated the impact of diabetes in the mortality of HF patients according to their age.

Methods We studied a cohort of chronic ambulatory HF patients prospectively recruited. Patients were on optimized evidence-based therapy, and they were excluded if on renal replacement therapy or if they had any therapy modification or hospitalizations in the previous 2 months. Patients were followed for up to 5 years; all-cause mortality was analyzed. Mortality predictors were assessed using a Cox regression. Analysis was stratified according to patient's age: cutoff 75 years. Multivariate models were built. Interaction between diabetes and age was formally tested.

Results We studied 283 chronic HF patients; mean age was 69 years and 70.3% were male; 58.0% had severe systolic dysfunction; 105 (37.1%) were diabetic. In patients with less than 75 years, the coexistence of diabetes predicted a multivariate adjusted 1.98 (95% CI 1.13–3.46) 5-year death risk while in older patients (≥ 75 years) no significant association was reported. Age interacted with the prognostic impact of diabetes, p for interaction = 0.04.

Conclusions The prognostic impact of diabetes in chronic HF depends on patient's age. In patients < 75 years, the coexistence of diabetes predicts an almost double risk of 5-year mortality; no such association exists in patients with 75 years or above. Diabetes predicts mortality only in younger HF patients.

Keywords Diabetes · Heart failure · Age · Prognosis

Introduction

Heart failure (HF) is a major health-care problem associated with high morbidity and mortality [1]. Increasing age is a major risk factor for HF [2] and a well-established prognostic determinant in chronic HF [3, 4]. Age appears to interact with other prognostic factors like systolic blood pressure [5] or atrial fibrillation [6]. Age may also modulate the impact of metabolic syndrome on arterial stiffness, known to be associated with HF [7, 8]. A higher comorbidity burden is a somehow expected consequence of increasing age, and it has been shown to associate with worse HF outcome [9, 10]. Nonetheless, the adverse effect of age appears to be independent of the comorbidities it frequently carries [11, 12].

The risk of diabetes *mellitus* (DM) also increases with age, and it is, as well, a known major risk factor for HF [13]. Diabetes is a frequently encountered comorbidity in chronic HF patients with an estimated prevalence of 24–50% [14, 15]; and HF is, likewise, a known risk factor for DM in part

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because it represents a condition that courses with insulin resistance [16]. There seems to be a bidirectional relationship between HF and DM, almost resembling a vicious cycle between the two clinical entities.

In the general population, diabetes alone is associated with increased mortality risk, mainly from cardiovascular disease [17, 18]. However, despite the striking association between diabetes and HF, the independent prognostic impact of DM in HF mortality is still a matter of some debate [19]. Diabetes has been mostly reported to be independently associated with increased HF hospitalization and mortality [14, 15, 20–28]; nevertheless, not all studies have found such association mostly in the acute HF setting [29–32].

Moreover, DM appears to interact with other prognostic factors such as left ventricular function [23]; and some studies suggest that its effect may be age and sex-dependent, with a sex-diabetes interaction only seen in younger patients in acute HF [33] and in older patients in chronic HF patients [34].

Despite the known impact of age in HF prognosis, the widely suggested impact of diabetes in HF outcome and the potential role of age in the prognostic impact of diabetes in HF, the differential impact of diabetes depending on patients' age was not formally studied in a contemporary HF patient population. We aimed to evaluate the impact of DM in the mortality of HF patients according to their age in a group of stable chronic HF patients with optimized HF therapy.

Methods

We conducted a prospective cohort study between May 2009 and January 2012. Patients followed in our HF clinic were recruited during scheduled medical visits. The diagnosis of HF was based on the 2008 European Society of Cardiology guidelines [35]. Patients with HF diagnosed for at least 6 months and with optimized evidence-based therapy were eligible for study inclusion. All patients had an echocardiogram performed in our hospital during the previous year. As a general reference, severe left ventricle systolic dysfunction corresponded to left ventricular ejection fraction lower than 30%, moderate systolic dysfunction to left ventricular ejection fraction between 30 and 39%, and mild to ejection fraction between 40 and 49%; patients with ejection fraction of at least 50% were considered to have preserved ejection fraction. We excluded patients with therapy modifications or hospitalizations in the previous 2 months and also patients on renal replacement therapy. Patients were screened for eligibility in the scheduled medical visits and recruited if the above conditions were met. A medical visit was then programmed for a morning in the following week where patients would be performed a complete physical examination and collected a fasting venous blood sample. B-type natriuretic peptide (BNP) determination is a routine laboratory procedure in our hospital; an Abbott chemiluminescent microparticle immunoassay (2-step immunoassay) is used. The measurement range of this assay is 10–5000 pg/mL. Serum sodium and creatinine were measured using conventional methods with an Olympus AU5400® automated clinical chemistry analyzer Beckman-Coulter®. Hemoglobin was obtained using an automated blood counter Sysmex® XE-5000. Comorbidities, demographic data and medications in use were registered. Comorbidities were defined as follows. Arterial hypertension was defined as the presence of previous diagnosis, record of antihypertensive pharmacological treatment or blood pressure above 140/90 mmHg. DM was defined as either a known previous diagnosis, current prescription of either an oral hypoglycemic agent or insulin, or a fasting venous blood glucose above 126 mg/dL, or a random glucose > 200 mg/dL. In addition, all patients with a glycated hemoglobin above 6.5% were also considered diabetic.

The protocol conforms to the ethical guidelines of the Declaration of Helsinki, and it was approved by the local ethics committee. Patients provided informed consent. Physicians treating HF patients were aware of the ongoing HF study. Patients' vital status and hospital admissions were ascertained by consulting hospital registries and by telephone contact with the patients or their relatives. Patients were followed for a 5-year period. The primary endpoint analyzed was all-cause death. Patients that needed heart transplantation were censored at transplantation date and considered as not achieving the primary endpoint.

Statistical analysis

A total of 283 patients were studied. Diabetics and non-diabetics were compared; comparison between patients < 75 years and those ≥ 75 is also shown: a Chi-square test was used for categorical variables, a student's *t* test for normally distributed continuous variables and a Mann–Whitney *U* test for continuous variables with a highly skewed distribution. A Cox regression analysis was performed to study variables with prognostic impact. A multivariate model was built based on variables shown to associate with 5-year mortality. Interaction between diabetes and age was formally tested. Analysis was then stratified according to patient's age—cutoff 75 years. Only variables with p value < 0.10 were retained in the final models. Kaplan–Meier method was used to show and compare survival curves according to diabetes separately in patients < 75 and those ≥ 75 years. The p value considered for statistical significance was 0.05. Data were stored and analyzed using SPSS software (IBM corp, Armonk, NY, version 20.0).

Results

We studied 283 stable chronic HF patients under optimized evidence-based therapy. Mean patient's age was 69 years and 70.3% were male; 58.0% of the patients had severe systolic dysfunction; 18.4% had moderate systolic dysfunction, 17.0% mild systolic dysfunction and 6.7% preserved ejection fraction. Median (interquartile range) BNP was 236.3 (113.0–627.0) pg/mL. One-hundred and five (37.1%) patients were diabetic. Diabetic patients were older and more often had concomitant arterial hypertension; they also had higher body mass index (BMI), lower hemoglobin and worse renal function. BNP was non-different among diabetics and non-diabetics, as well as no differences were reported concerning evidence-based therapy; diabetic patients were, however, more often medicated with statins and acetylsalicylic acid. During the 5-year follow-up period 134 (47.3%) patients died: 42.7% in non-diabetics and 55.2% in diabetics, p value 0.04. One patient was transplanted 539 days after enrollment. Table 1 shows the comparison between diabetic and non-diabetic patients. One-hundred and seventeen (41.3%) patients were 75 years or older. Older patients were more often hypertensive women in higher NYHA classes; they had lower BMI, lower hemoglobin and sodium as well as worse renal function and higher BNP. Older patients were less often on angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, and 5-year mortality was significantly higher among them (Table 1).

Table 2 shows variables associated with 5-year mortality in a univariate and multivariate approach. Age interacted with the prognostic impact of diabetes, p for interaction = 0.04. Analysis was then stratified according to patients' age: < 75 and ≥ 75 years, and the independent prognostic impact of diabetes was studied using multivariate Cox regression models. Variables considered in the model were only those with p value < 0.10 in the multivariate model shown in Table 2; the differential association of diabetes with 5-year mortality according to patients age is depicted in Table 3. In patients with less than 75 years, the coexistence of diabetes predicted a multivariate adjusted 1.98 (95% CI 1.13–3.46) 5-year death risk, while in older patients (≥ 75 years) no significant association was reported (HR 0.90, 95% CI 0.55–1.46, p value = 0.66). There was, in fact, a higher overall mortality among non-diabetics (70.0%) than among diabetics (57.4%) in this age strata; this was valid for both early and late mortality; however, the

Table 1 Comparison between diabetic and non-diabetic patients (left) and comparison between patients younger than 75 years and those with ≥ 75 years (right)

	Non-diabetics $n = 178$	Diabetics $n = 105$	p	< 75 years $n = 166$	≥ 75 years $n = 117$	p
Male gender, *n* (%)	127 (71.3)	72 (68.6)	0.62	127 (76.5)	72 (61.5)	0.007
Age (years), mean (SD)	67 (15)	72 (10)	0.004			
Diabetes *mellitus*, *n* (%)				58 (34.9)	47 (40.2)	0.37
Arterial hypertension, *n* (%)	96 (53.9)	61 (77.1)	< 0.001	88 (53.0)	89 (76.1)	< 0.001
Atrial fibrillation, n (%)	75 (42.1)	41 (39.0)	0.61	65 (39.2)	51 (43.3)	0.46
Severe dysfunction, *n* (%)	103 (62.0)	61 (62.2)	0.98	102 (65.0)	62 (57.9)	0.25
NYHA class ≥ II, *n* (%)	122 (68.5)	73 (69.5)	0.86	95 (57.2)	100 (85.5)	< 0.001
Systolic blood pressure (mmHg), mean (SD)	120 (20)	123 (21)	0.22	120 (21)	122 (20)	0.51
Heart rate (bpm), mean (SD)	72 (11)	71 (10)	0.28	72 (10)	72 (11)	0.85
Body mass index (kg/m^2), mean (SD)	26.7 (4.8)	27.9 (5.0)	0.04	28.1 (5.2)	25.8 (4.2)	< 0.001
Hemoglobin (g/dL), mean (SD)	13.2 (1.8)	12.6 (1.9)	0.01	13.4 (1.7)	12.4 (1.9)	< 0.001
Creatinine (mg/dL), mean (SD)	1.22 (0.41)	1.33 (0.44)	0.03	1.17 (0.40)	1.39 (0.43)	< 0.001
Serum sodium (mmol/L), mean (SD)	139 (3)	139 (3)	0.59	138 (3)	140 (3)	< 0.001
BNP (pg/mL), median (IQR)	210.6 (107.7–568.5)	298.0 (117.2–722.9)	0.17	160.8 (82.4–464.2)	60.2 (181.4–782.9)	< 0.001
Beta blocker, *n* (%)	171 (96.1)	99 (94.3)	0.49	161 (97.0)	109 (93.2)	0.22
ACEi/ARB, *n* (%)	166 (93.3)	96 (91.4)	0.57	159 (95.8)	103 (88.0)	0.01
Statin, *n* (%)	106 (59.96)	89 (84.9)	< 0.001	105 (63.3)	90 (76.9)	0.01
Acetylsalicylic acid, *n* (%)	50 (28.2)	63 (60.0)	< 0.001	58 (34.9)	55 (47.4)	0.04
Death at 5 years, *n* (%)	76 (42.7)	58 (55.2)	0.04	58 (34.9)	76 (65.0)	< 0.001

ACEi angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* B-type natriuretic peptide, *NYHA* New York Heart Association, *SD* standard deviation, *IQR* interquartile range

Table 2 Five-year mortality predictors: univariate approach (left) and multivariate analysis (right)

	HR (95% CI)	Wald	*p* value	HR (95% CI)	Wald	*p* value
Male gender	1.02 (0.70–1.48)	0.009	0.92			
Age (per year)	1.05 (1.03–1.06)	39.66	< 0.001			
Age ≥ 75 years	2.47 (1.75–3.48)	26.57	< 0.001	2.28 (1.34–3.88)	9.23	0.002
Diabetes *mellitus*	1.39 (0.99–1.96)	3.60	0.06	1.84 (1.06–3.21)	4.62	0.03
Arterial hypertension	1.41 (0.98–2.03)	3.46	0.06	1.08 (0.71–1.65)	0.14	0.71
Atrial fibrillation	1.58 (1.13–2.22)	7.08	0.008	1.17 (0.82–1.68)	0.73	0.39
Severe dysfunction	1.28 (0.88–1.86)	1.62	0.20			
NYHA class ≥ II	2.82 (1.80–4.42)	20.43	< 0.001	1.53 (0.93–2.52)	2.78	0.096
Systolic blood pressure (per 10 mmHg)	0.93 (0.85–1.01)	2.67	0.10			
Heart rate (per 10 bpm)	1.07 (0.90–1.27)	0.59	0.44			
Body mass index (per kg/m^2)	0.97 (0.94–1.00)	2.92	0.09	0.98 (0.94–1.02)	0.74	0.39
Hemoglobin (per g/dL)	0.86 (0.79–0.94)	10.77	0.001	0.94 (0.86–1.04)	1.50	0.22
Creatinine (per mg/dL)	3.16 (2.26–4.42)	45.30	< 0.001	1.82 (1.23–2.69)	8.87	0.003
Serum sodium (per mmol/L)	0.96 (0.90–1.02)	1.92	0.17			
BNP > 225 pg/mL	3.82 (2.60–5.61)	46.79	< 0.001	2.28 (1.48–3.52)	14.14	< 0.001
Beta blocker (per 6.25 mg carvedilol equivalent)	0.92 (0.86–0.98)	6.06	0.01	1.04 (0.97–1.12)	1.16	0.28
ACEi/ARB (per 5 mg lisinopril equivalent)	0.75 (0.66–0.84)	22.60	< 0.001	0.86 (0.75–0.98)	5.15	0.02
Interaction diabetes mellitus_age ≥ 75 years						0.04

Only variables with *p* value < 0.010 were included in the multivariate analysis

ACEi angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* B-type natriuretic peptide, *CI* confidence interval, *HR* hazard ratio, *NYHA* New York Heart Association

Table 3 Five-year mortality predictors: multivariate models

	< 75 years			≥ 75 years		
	HR (95% CI)	Wald	*p* value	HR (95% CI)	Wald	*p* value
Model 1						
Diabetes *mellitus*	1.98 (1.13–3.46)	5.70	0.02	0.90 (0.55–1.46)	0.19	0.66
NYHA class ≥ II	1.39 (0.76–2.54)	1.14	0.28	1.87 (0.80–4.40)	20.80	0.15
Creatinine (per mg/dL)	1.68 (0.95–2.97)	3.17	0.08	1.99 (1.19–3.34)	6.84	0.009
BNP > 225 pg/mL	2.56 (1.39–4.70)	9.10	0.003	2.36 (1.31–4.25)	8.13	0.004
ACEi/ARB (per 5 mg lisinopril equivalent)	0.91 (0.75–1.10)	1.01	0.32	0.86 (0.74–1.00)	3.80	0.05
Model 2						
Diabetes *mellitus*	1.87 (1.06–3.31)	4.63	0.03	0.92 (0.54–1.54)	0.11	0.74
NYHA class ≥ II	1.37 (0.73–2.58)	0.95	0.33	1.90 (0.79–4.55)	20.60	0.15
Creatinine (per mg/dL)	1.73 (0.97–3.09)	3.48	0.06	2.27 (1.30–3.94)	8.43	0.004
BNP > 225 pg/mL	2.62 (1.41–4.88)	9.24	0.002	2.39 (1.31–4.34)	8.15	0.004
ACEi/ARB (per 5 mg lisinopril equivalent)	0.88 (0.72–1.07)	1.74	0.19	0.89 (0.76-1.04)	2.10	0.15
Hemoglobin (per g/dL)	0.94 (0.81–1.09)	0.73	0.39	0.94 (0.83–1.05)	1.18	0.28
Body mass index (per kg/m^2)	1.01 (0.96–1.07)	0.10	0.76	0.95 (0.89–1.01)	2.67	0.10
Beta blocker (per 6.25 mg carvedilol equivalent)	1.06 (0.96–1.18)	1.29	0.26	1.00 (0.89–1.12)	0.001	0.97

Analysis is stratified according to patients age (< 75 and ≥ 75 years)

ACEi angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* B-type natriuretic peptide, *CI* confidence interval, *HR* hazard ratio, *NYHA* New York Heart Association

difference was not significant and non-diabetic patients were older than diabetic ones: 81 (IQR: 78–84) versus 78 (76–82), *p* value = 0.02. If hemoglobin, BMI and beta blocker dose were also considered in the model, results were similar. Figure 1 shows the Kaplan–Meier survival curves according to the coexistence of diabetes separately in patients younger

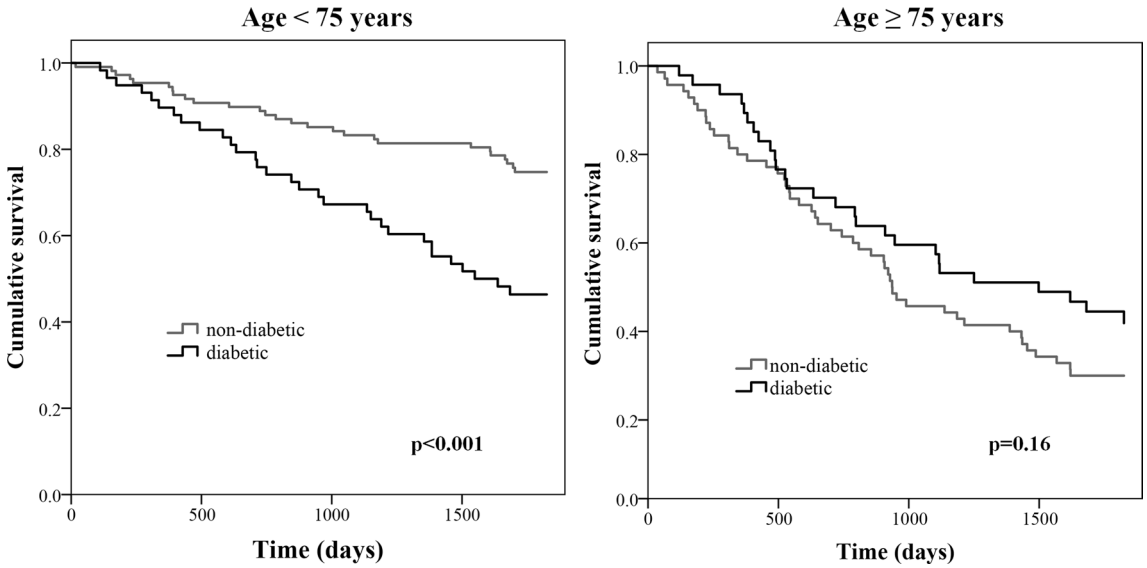

Fig. 1 Kaplan-Meier survival curves in diabetics and non-diabetics separately in patients < 75 years (left) and patients with ≥ 75 years (right). Diabetes only predicted higher 5-year mortality in younger patients

and older than 75 years. Diabetes predicted mortality only in younger HF patients.

Discussion

In our population of stable chronic HF patients, diabetic patients had a higher 5-year all-cause mortality compared with non-diabetic patients. The prognostic effect of diabetes was only observed in patients younger than 75 years old with a significant interaction between diabetes and age. In patients < 75 years diabetes associated with an almost two-fold higher 5-year death risk, diabetes was not independently associated with outcome in older patients.

Older patients are a large, increasing, and particular group of HF patients [1, 36, 37]. Since older patients were consistently excluded from the large therapeutic trials in HF, doubts persist concerning their characteristics and specificities [37]. Age is not only an independent predictor of a bleak prognosis in HF, but it also appears to influence the effect of other HF prognostic determinants such as blood pressure [5] and atrial fibrillation [6]. In acute HF, lower systolic blood pressure associates with higher mortality risk especially in the elder [5]. In chronic HF, on the contrary, the presence of atrial fibrillation is an independent death predictor only in patients younger than 75 years [6]. Interestingly, even the effect of age was affected by age itself, with increasing age predicting higher death risk only in HF patients older than 75 years [38]. A potential effect of age in the prognostic impact of diabetes in HF has been suggested [33, 34] but, as far as extensive literature review could retrieve, was never tested with formal interaction terms.

The coexistence of DM associates with an ominous outcome in chronic HF [14, 15, 19, 21, 22, 24, 25]. Its prognostic role in the acute setting is less well established and discrepancies between in-hospital mortality and post-discharge outcomes have been reported [20, 23, 26–31]. Diabetes may be outcome associated only in certain groups of patients [23, 28, 33, 34]. An incremental prognostic worsening in diabetics compared with non-diabetics across left ventricular function strata in HF has been reported [23]. A sex–diabetes interaction has been reported as well [28, 33, 34]: not only diabetic women have an increased risk of incident HF, but also seem to have higher mortality than men once HF is established [13, 28].

A possible influence of age in the prognostic impact of diabetes in HF has been previously suggested [33, 34]. In a pre-beta blocker chronic HF population of almost eight thousand patients of the Digitalis Investigation Group trial, Ahmed et al. [34] reported that diabetes was associated with increased mortality in both men and women under 65 years but only in women above that age. MacDonald et al. [33] studied over 110 thousand patients post-hospitalization due to acute HF. Diabetics had higher 1-year mortality, and the death risk associated with DM was greatest in patients ≤ 65 years. A diabetes–sex interaction was reported in the younger group of patients with significantly higher risk among women. Our study has clear differences from those addressing the issue of a potential differential effect of diabetes in HF prognosis according to age, and therefore results are not directly comparable. The study from Ahmed

et al. [34] in chronic HF was a propensity matched study in HF patients before the generalized use of beta blockers, so it does not represent a contemporary HF population; besides, patients were much younger also reflecting a globally different population than that corresponding to nowadays HF reality. The study from MacDonald et al. [33] was a large Scottish study performed in an acute HF setting and also included predominantly pre-beta blocker and pre-angiotensin-converting-enzyme inhibitor HF patients; besides that the reported prevalence of DM, 13%, is extremely low when compared with contemporary HF populations [14, 15]. It is also important to note that interaction between age and diabetes was not formally tested in neither of these previous studies. Because of our small sample size, we could not further stratify diabetic and non-diabetic patients according to gender. Still, if gender was also included in our multivariate model, diabetes remained an independent mortality predictor only in younger patients (data not shown) with significant age–diabetes interaction (p for interaction = 0.04)

Our study has other limitations that are important to refer. It is a single center study with generalisability issues. Also, despite the prospective recruitment of chronic HF patients as part of a chronic HF registry, this particular analysis is retrospective in nature and therefore with inherent concerns related with missing data and lack of information. Some unknown/unavailable or insufficient data concerning factors not accounted for may have influenced our results. The diabetes' duration, the metabolic control and anti-hyperglycemic therapy prescribed were not taken into consideration and may have contributed to the results obtained. One should remember that older patients might have been exposed to the disease for longer periods, might have been treated differently, in part because some therapies have a more favorable safety profile in the elder, and might have had a diverse metabolic control; all these variables could have been of potential impact on the outcome of interest.

DM is more than a categorical variable. It encompasses a continuum of glycaemic control, multiple progressive micro- and macrovascular complications and additive and escalating anti-hyperglycemic therapies with different cardiovascular effects. All of these factors have been shown to affect outcomes, namely cardiovascular outcomes [39–42]. Older patients with DM have been shown to have a better disease control and a better control of other cardiovascular risk factors than their younger counterparts [43, 44]. This lack of association of DM with mortality in the elder may reflect an overall better metabolic and other cardiovascular risk factors control in senior patients; this hypothesis could not be tested due to quality of data restraints. In the elder group of patients there was, in fact, a higher overall mortality among non-diabetics than among diabetics; however, the difference was not significant and it may have been in part due to the fact that non-diabetics were older than diabetics. This reinforces the idea that in elder patients, age itself is a more important outcome determinant than diabetes.

In addition, arterial stiffness, a known cardiovascular risk factor, is increased in diabetic patients of all ages [45]. Therefore, diabetic patients show "aged" vascular structures at younger chronological ages; this could be an explanation for our findings. The relationship between metabolic syndrome and arterial stiffness appears to be modulated by age, and be diverse for the various arterial stiffness components [7]; the role of arterial stiffness also appears to vary depending on age [46]. The results of our study suggest that in older patients, the effect of diabetes as a component of metabolic syndrome may have a decreasing impact on arterial stiffness as age progresses eventually because age alone has an already very strong effect on the vasculature.

Our results reinforce a role for age in HF. Although in the whole study sample diabetes conferred survival disadvantage, that association was only applicable to patients younger than 75 years. In older patients, age is a sufficiently strong and almost overwhelming risk factor per se and diabetes may fail to add to their ominous fate while, in younger patients, diabetes and its unfavorable metabolic and structural effects still have pathophysiologic legacy to impact prognosis. A similar phenomenon has already been reported for other variables/risk factors such as in atrial fibrillation [6] and is in line with the overall softening of cardiovascular risk factors management, like blood pressure and cholesterol levels, as age progresses [47, 48]. Even the proposed target in diabetes control is more permissive as age increases [49]. The major suggestion of our study is that at older ages focus should probably be shifted toward functional status and quality of life rather than "usual" medical parameters.

Conclusions

Diabetes associates with higher mortality in chronic HF patients < 75 years; however, it does not impact prognosis in the elder. This difference in prognostic impact is significant and attributable to age itself. Elder patients are a very particular group of patients with specificities in care that need to be better defined.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights disclosure This study is in accordance with the ethical standards of the institutional ethical committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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