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Screening for heart failure in individuals with diabetes: *a cross-sectional study*

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ABSTRACT

Objective. *Heart failure (HF) is a common and serious co-morbidity of diabetes, because of high prevalence and poor prognosis. Previous data showed that heart failure is significantly under-diagnosed in the current practice from our country. In this study we aimed to determine the prevalence of diagnosed heart failure in individuals with diabetes and to perform a screening for heart failure, using a method that can be easily applied in real-practice conditions.*

Method. *We conducted a cross-sectional study on an unselected population of patients with diabetes attending an outpatient clinic. Subjects underwent a complete interview (including symptoms of HF) and clinical exam, followed by a rest ECG. Positive screening for HF (suspected new heart failure) was established based on the combination of positive symptoms (at least two symptoms- dyspnea, tiredness, or ankle edema) and significant ECG changes (Q-wave myocardial infarction, left bundle branch block, or left ventricular hypertrophy).*

Results. *The study sample consisted of 211 patients with diabetes, with a mean age of 58.8 ±10.2 years; 118 (55.9%) were men, and 199 (94.3%) had type 2 diabetes. Prevalence of previously-diagnosed HF was 5.7% and "suspected new heart failure" was identified in 27 (12.8%) of patients in the study group. When cases with previous diagnosis of HF were added to those identified by the screening protocol, the total prevalence of HF in our study group was 18.5%. The following factors were found to be significantly associated with the presence of "suspected new heart failure": body mass index (BMI) ≥ 30 kg/m^2 (OR 3.42, 95%CI 1.37-8.58, p=0.008), glomerular filtration rate (GFR) < 60 mL/min/1.73 m < (OR 3.94, 95%CI 1.58-9.79, p=0.003), and presence of hypertension (OR 9.49, 95%CI 1.25-71.9, p=0.029), ischemic heart disease (OR 3.63, 95%CI 1.58-8.36, p=0.002), atrial fibrillation (OR 7.04, 95%CI 1.34-36.9, p=0.021), peripheral artery disease (OR 5.25, 95%CI 1.10-24.9, p=0.037) and metabolic syndrome (OR 2.54, 95%CI 1.02-6.32, p=0.045).*

Conclusion*. Presence of HF in our study group of patients with diabetes is under-estimated when based on patients' history. The active screening for HF, using a simple and accessible protocol for a diabetes outpatient clinic, more than doubles the number of HF cases. This would allow a larger number of patients to benefit from preventive strategies that might reduce HF-related deaths and hospitalization for exacerbation of HF episodes.*

Keywords: diabetes, heart failure, screening

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BACKGROUND

Heart failure (HF) is a common and serious co-morbidity of diabetes. Data from the Framingham Heart Study showed, over 20 years ago, that HF was two times as common in diabetic men and five times as common in diabetic women aged 45-74 years than in age-matched control subjects. This association was even stronger in younger patients (ages≤65 years), being fourfold higher in diabetic men and eightfold higher in diabetic women than in non-diabetic subjects (1). More recent studies reported prevalence of heart failure in individuals with diabetes ranging from 11.8% in the cohort from Kaiser Permanente Northwest Division (2) and in the Reykjavik study (3) to 22.3% in a cohort of elderly (≥ 65 years of age) patients with diabetes (4). In NHANES-I (National Health and Nutrition Examination Survey) Epidemiological Follow-up Study, the cumulative incidence of heart failure at the age of 85 years was found to be 65.5% in men with diabetes compared with 36.9% in men without diabetes, and 61.8% in women with diabetes compared with 28.9% in those without diabetes (5).

Patients with diabetes account for more than 33% of all patients requiring hospitalization for HF (6), and represent about 25% of all patients enrolled in large-scale clinical trials evaluating treatments for HF: 23% in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), 25% in Studies of Left Ventricular Dysfunction (SOLVD) trial, 20% in Assessment of Treatment with Lisinopril and Survival (ATLAS) study, and 27% in Randomized Evaluation for Strategies of Left Ventricular Dysfunction (RESOLVD) study (7-10).

Information on the association of diabetes and heart failure in our country is very limited. In a retrospective study on patients with diabetes admitted in an in-patient department, the prevalence of previously-diagnosed HF was 5.1%. When medical records have been reviewed for the presence of suggestive symptoms and objective evidence of cardiac impairement (ECG, chest X-ray and/or cardiac ultrasonography), another 2% of patients have been retrospectively diagnosed with HF, resulting in a total prevalence of 7.1% heart failure cases for in-patients with diabetes. This figure was considered very low for a selected population with diabetes, as it is the case with hospitalized patients, and we concluded that heart failure is clearly under-diagnosed in individuals with diabetes in current practice (11).

The objectives of the present study are to determine the prevalence of diagnosed heart failure in individuals with diabetes and to perform a screening for heart failure, using a method that can be easily applied in real-practice conditions. ❑

METHODS

We conducted a cross-sectional study on an unselected population of patients with diabetes attending the outpatient clinic from the Clinical Center of Diabetes, Nutrition and Metabolic Diseases of Cluj-Napoca. The sample size was calculated using the Cochran equation (12) to obtain a 95% confidence interval of ± 5% around a prevalence estimate for heart failure of 15%, resulting in a number of 196 subjects to be included in the study group.

The first 2 patients presenting daily for the routine visits in the outpatient department and who accepted study procedures were included in the study from March 1 to September 1, 2007. Patients have been assessed for demographic characteristics, diabetes history (type and duration of diabetes, diabetic complications, anti hyperglycemic treatment), personal history for cardiovascular diseases (including previous diagnosis of heart failure, level of physical activity (low, medium, high), and treatment with cardiovascular medications. Anthropometric parameters (weight, height, and waist circumference, as well as systolic and diastolic blood pressure after a 5 minute rest have been measured. Body mass index (BMI) was calculated as weight (kg)/ [height (m)]^2. A rest 12-leads ECG has been performed in all patients. Patients underwent a fasting blood testing for blood glucose, hemoglobin A1c, total cholesterol, HDL-cholesterol, serum triglycerides, and serum creatinine. Microalbuminuria has been determined from an overnight urine sample in a subset of the study population. Renal dysfunction was assessed by calculated glomerular filtration rate (GFR):

$$GFR\ (mL/min/1.73\ m^2) = 186 \times (Serum\ creatinine)^{-1.154} \times (Age)^{-0.203} \times (1.21\ if\ Black) \times (0.742\ if\ female)$$ (13).

Metabolic syndrome was diagnosed according to International Diabetes Federation (IDF) criteria (14).

"Suspected new heart failure" (positive screening for heart failure) was diagnosed as the combination of at least two symptoms (dyspnea, tiredness, or ankle edema) and one objective evidence of cardiac engagement, as disclosed by the ECG (Q-wave myocardial infarction according to MONICA [Monitoring Cardiovascular Disease] criteria, left bundle branch block, or left ventricular hypertrophy). Presence of LVH was defined by Sokolow-Lyon ECG criteria (R wave in V5 through V6+S wave in V1 >35 mm), Cornell voltage criteria (R wave in aVL+ S wave in V3 >20 mm in women or >28 mm in men), or both. ❑

Statistical analysis

SPSS-PC 13.0 (SPSS Inc., Chicago, IL, USA) package was used for statistical analysis.

To detect significant differences between variables, t-test was used for normally distributed data, Man-Whitney U test for variables with abnormal distribution and Fisher's exact test for categorical variables. Logistic regression served to obtain the odds ratios for factors associated with the presence of newly-diagnosed cases of heart failure. All reported *P* values are two sided, and a *P* value <0.05 was considered to indicate statistical significance.

RESULTS

The study sample consisted of 211 patients with diabetes, with a mean age of 58.8 ±10.2 years; 118 (55.9%) were men, and 199 (94.3%) had type 2 diabetes. The main characteristics of the study group are shown in Table 1. Men and women had similar characteristics, except significantly higher waist circumference and creatinine levels in men. As well, significantly more men are current or ex-smokers.

Use of anti hyperglycemic treatments in patients with type 1 and type 2 diabetes is shown in Figure 1. From the entire study group, 43.6%

	Total
Number	211
Men (%)	55.9
Age (years)	58.8±10.2
Smoking n, (%)	
Non smokers	133±63.0
Ex-smokers	49±23.2
Current smokers	29±13.7
Level of physical activity n, (%)	
Low	93±44.1
Medium	105±49.8
High	13±6.2
Type of diabetes n, (%)	
Type 1	12±5.7
Type 2	199±94.3
Duration of diabetes† (years)	5 (3;9)
BMI (kg/m²)	29.9 ±5.7
Waist circumference (cm)	106 ±13.1
Systolic blood pressure (mmHg)	140.6±23.4
Diastolic blood pressure (mmHg)	82.3±12.5
Fasting blood glucose (mg/dL)	159 (123.5; 181)
HbA1c (%)	7.4 ±1.5
Total cholesterol (mg/dL)	192.0±39.7
HDL cholesterol (mg/dL)	44.0±12.1
Serum triglycerides (mg/dL)	212.0±130.1
Serum creatinine† (mg/dL)	1.0 (0.8;1.12)
Glomerular filtration rate (ml/min/1.73 m²)	73.77±17.06
Microalbuminuria† (μg/dL)	22.5 (15;47.5)

TABLE 1. Main characteristics of the study group

Data in table is presented as means±SD, unless specified otherwise; † Variables with abnormal distribution are presented as median (1st quartile; 3rd quartile)

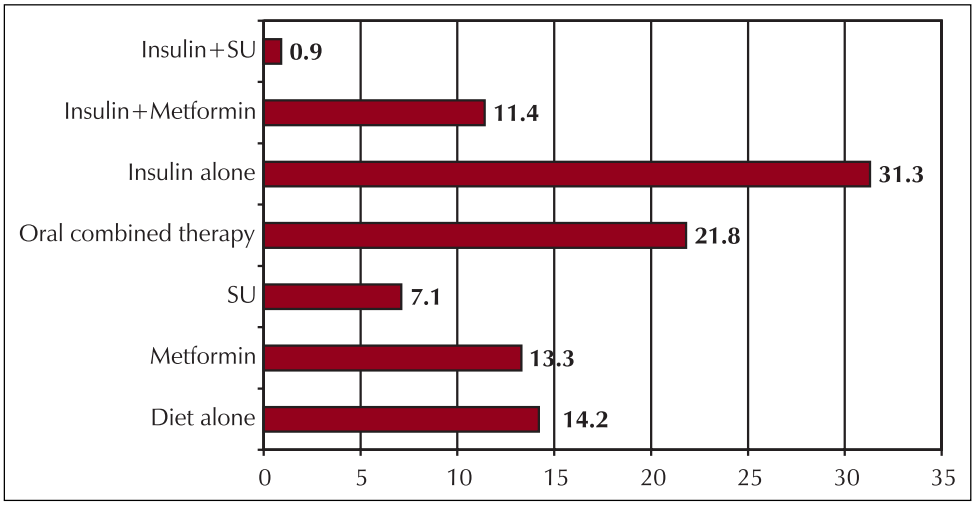

FIGURE 1. Use of anti hyperglycemic treatments among subjects included in the study

Data is shown as %; SU, sulphonylureea

of the patients were treated with insulin, alone or in combination with oral agents. When patients with type 1 diabetes were excluded from the analysis, the percentage of insulin-treated type 2 diabetes was 40.2%.

Prevalence of specific diabetes complications was as follows: 28.9% of subjects had diabetic retinopathy, 37% had peripheral diabetic neuropathy, and 54.4 % had an abnormal albumin excretion rate (≥20 μg/dL in an overnight urine sample). Renal dysfunction (GFR< 60 mL/min/1.73m^2) was present in 38 patients, representing 18.9% of the study population.

History of cardiovascular diseases, presence of other associated conditions (overweight/obesity, dyslipidemia, metabolic syndrome) and use of cardiovascular medication were obtained from the medical records existing at the outpatient clinic, and were confronted with patients' interviews and other medical records from Cardiology, Neurology or Internal Medicine departments whenever possible. Prevalence of cardiovascular diseases (including previous diagnosis of chronic heart failure) and associated conditions are shown in Figure 2. 68 patients (32.2%) had ischemic heart disease from whom 16 patients (7.6% of study group) had a history of myocardial infarction. Prior diagnosis of congestive heart failure was found in 12 (5.7%) of patients included in the study group. Over 70% of patients had hypertension, dyslipidemia and/or overweight/obesity (defined as a BMI ≥ 25 kg/m^2). Metabolic syndrome, diagnosed according to the International Diabetes Federation set of criteria (14), was present in 68.3% of the patients.

Use of cardiovascular medication in the overall study group is displayed in Table 2. The most frequently used class of drugs were RAAS inhibitors (60.2%), with a relative high percentage of patients being treated with beta blockers (41.2%) and a small number of patients treated with digoxine (3 patients- 0.5%). Statins and fibrates are clearly underused (38.9% and 16.1% respectively) since over 70% of patients had been diagnosed with a form of dyslipidemia.

Patients were interviewed for the presence of dyspnea, tiredness and ankle edema and a physical examination was performed for the latter criterian (patients with prior diagnosis of

	% of patients
RAAS blockers (ACEI or ARB)	60.2
Beta blockers	41.2
Calcium-channel blockers	18.5
Diuretics (including indapamide)	37.4
Digoxine	0.5
Aspirin	39.3
Statins	38.9
Fibrates	16.1

TABLE 2. Use of cardiovascular medications

RAAS, renine-angiotensine-aldosteron system; ACEI, angiotensine converting-enzyme inhibitor; ARB, angiotensine receptor blocker

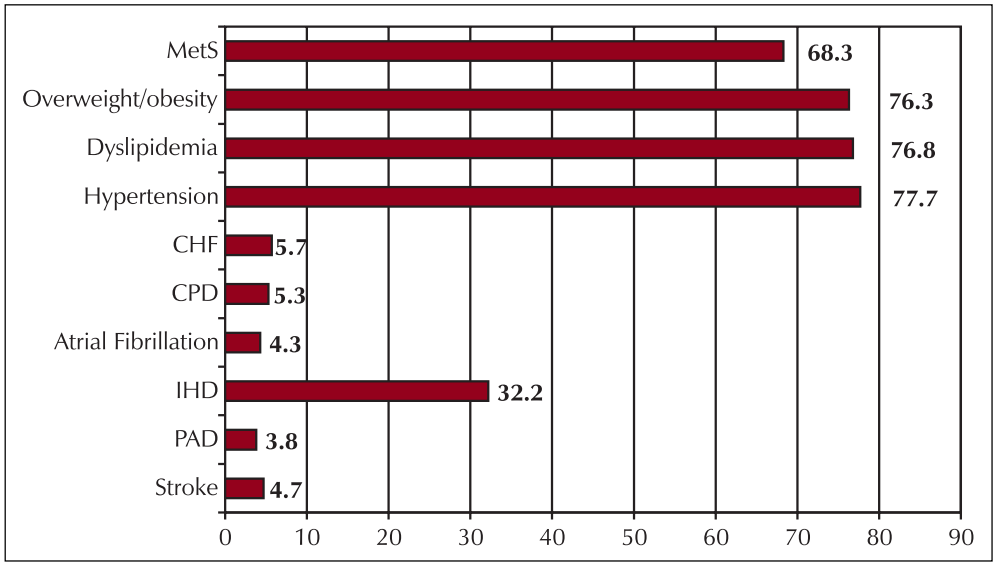

FIGURE 2. Prevalence of cardiovascular diseases and associated conditions

Data is shown as %; PAD, peripheral artery disease; IHD, ischemic heart disease; CPD, chronic pulmonary disease; CHF, congestive heart failure; MetS, metabolic syndrome

heart failure were not included). A total of 89 patients (42.2%) had a degree of dyspnea, 92 (43.6%) recognized the presence of tiredness at exertion or at rest, and 50 (23.7%) had ankle edema. The combination of at least two of the above symptoms occurred in 34 (16.1%) of patients, which were considered "positive for symptoms". Significant ECG changes (Q wave MI, left bundle branch block and/or left ventricular hypertrophy) were found in 56 (26.5%) of patients; 21 patients (10.5%) had Q wave MI, 31 (15.6%) had left ventricular hypertrophy and 4 (2%) had both ECG changes.

The combination of positive symptoms and significant ECG changes was found in 27 (12.8%) of patients in the study group (Figure 3), these patients being classified as "positive for heart failure screening" and representing suspected new heart failure cases. When cases with previous diagnosis of HF were added to those newly-diagnosed, the total prevalence of HF in our study group was 18.5%.

Variables included in the database were tested for significance in patients with or without "suspected new heart failure". The following factors were found to be significantly associated with the presence of "suspected new heart failure": BMI ≥ 30 kg/m², GFR < 60 mL/min/1.73 m², and presence of hypertension, ischemic heart disease, atrial fibrillation, peripheral artery disease and metabolic syndrome. Odds ratio, 95% CI and statistical significance are represented in Table 3. ❑

DISCUSSIONS

The prevalence of previously-diagnosed heart failure in our study population was 5.7%, very low when compared with the data from the literature: 11.8% in the cohort from Kaiser Permanente Northwest Division (2) and in the Reykjavik study (3) and 22.3% in a cohort of elderly (≥ 65 years of age) patients with diabetes (4).

Studies on heart failure in individuals with diabetes had different methods to assessing the presence of heart failure which are important when comparing prevalence data.

In the study of Nichols et al (2), the prevalence of HF was based on the presence of ICD-9-CM (Intenational Classification of Diseases, Ninth Revision, Clinical Modification) diagnosis codes for heart failure in an unselected population of over 9,000 patients with type 2 diabetes who were older (mean age 64.2 years), but with less hypertension (52.5 vs 77.7%) and ischemic heart disease (25.1 vs 32.2%), less use of insulin (19.7 vs 43.6%), and similar levels of A1c, systolic and diastolic blood pressure when compared with our study population. The reported prevalence of HF was 11.8%, almost double than in our study, which included higher-risk patients in terms of presence of ischemic heart disease, hypertension and use of insulin; this data confirms that in our

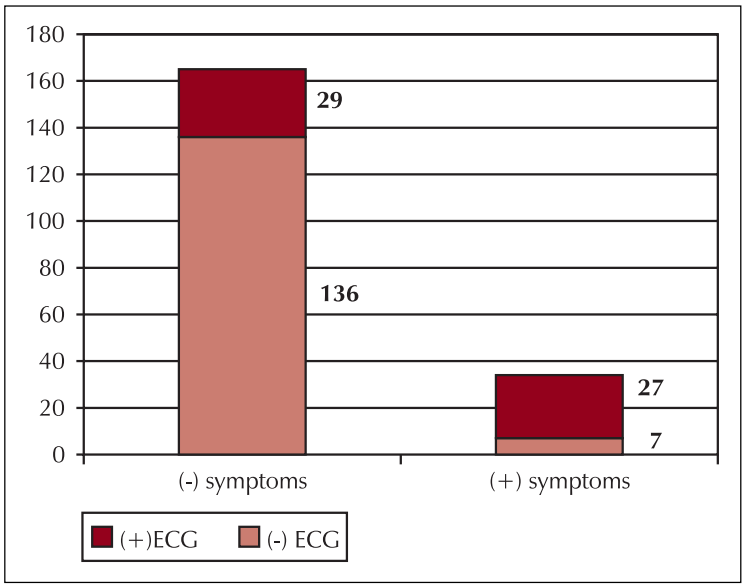

FIGURE 3. Combined findings of patients "positive for symptoms" and "with significant ECG changes". Data is shown as number of patients in each category

Legend Figure 3:
(-) symptoms, negative for symptoms e.g. one or no symptoms for HF (dyspnea, tiredness, or ankle edema)
(+) symptoms, positive for symptoms e.g. at least two symptoms (dyspnea, tiredness, or ankle edema)
(+) ECG, significant ECG changes e.g. Q wave MI and/or left ventricular hypertrophy
(-) ECG, one or none of the following: Q wave MI and left ventricular hypertrophy
MI, myocardial infarction

	OR	95% CI	p
BMI ≥ 30 kg/m²	3.42	1.37-8.58	0.008
GFR< 60 mL/min/1.73 m²	3.94	1.58-9.79	0.003
Peripheral artery disease	5.25	1.10-24.9	0.037
Atrial fibrillation	7.04	1.34-36.9	0.021
Ischemic heart disease	3.63	1.58-8.36	0.002
Metabolic syndrome	2.54	1.02-6.32	0.045
Hypertension	9.49	1.25-71.9	0.029

TABLE 3. Factors associated with "suspected new heart failure" in logistic regression models, adjusted for age and sex

population with diabetes, HF is significantly under-diagnosed.

In NHANES I Epidemiologic Follow-up Study (5) prevalent heart failure was defined as "ever being told by a physician that they have had heart failure or having used medications for a *weak heart* during 6 months before baseline interviews", and incident heart failure was considered if the patient had a discharge diagnosis or a death certificate with the ICD-9 (International Classification of Diseases, Ninth Revision) code of 428.0 to 428.9. The study did not report data on prevalence of heart failure in patients with diabetes, as did our study.

Reykjavik study (3) was a population-based cohort study which recruited 19,381 participants aged 33–84 years over a 30-year period (1967-1997) who were followed until 2002 and examined the prevalence of HF according to categories of glucose tolerance. Cases were defined in accordance with World Health Organization criteria for type 2 diabetes or abnormal glucose regulation (impaired glucose tolerance or impaired fasting glucose) and European Society of Cardiology guidelines for heart failure (15), but considering the outcome of ECG or chest X-ray as objective evidence for cardiac dysfunction, and not echocardiogram (because of limited availability of the latter method). The investigators of the Reykjavik study recognized that there is a risk for false-positive and -negative diagnosis. However, in the Framingham Study, signs of cardiac dysfunction, such as heart enlargement on chest X-ray and left ventricular hypertrophy on ECG, were highly predictive for deteriorating cardiac function (16). Moreover, only 8–15% of asymptomatic people with hypertension, diabetes, coronary artery disease, or previous myocardial infarction had systolic dysfunction when screened with echocardiography (17).

We chose to further modify the protocol used in the Reykjavik study, considering that chest X-ray is less accessible for an out-patient diabetes clinic. In order to increase the sensitivity of ECG changes, we diagnosed left ventricular hypertrophy (LVH) as the presence of Sokolow-Lyon ECG criteria (R wave in V5 through V6+S wave in V1 >35 mm), Cornell voltage criteria (R wave in aVL+ S wave in V3 >20 mm in women or >28 mm in men), or both. These criteria have been chosen according to a recently published study (18) which showed that in 3074 patients with LVH as determined by echocardiogram, 978 (31.8%) met both LVH criteria, 1244 (40.5%) met Cornell criteria only, and 852 (27.7%) met Sokolow-Lyon criteria only.

The prevalence of HF in the subgroup of subjects with diabetes in the Reykjavik study was 12%, compared with 18.5% in our study which did not use chest X-ray as an objective sign of cardiac impairment, but only ECG changes. Nevertheless, it must be noted that some patients in the Reykjavik study had been diagnosed with diabetes during the study, according to oral glucose tolerance test or fasting blood glucose, while in our study group we included patients with known diabetes, having a median duration of 5 years.

Factors associated with prevalent and incident HF in the study of Nichols et al. were age, duration of diabetes, insulin treatment, ischemic heart disease, and high levels of serum creatinine (2). Other studies reported that nephropathy, peripheral artery disease (4), urinary albumin excretion, hemoglobin A1c (19), or fasting blood glucose (20) are factors associated with HF in individuals with diabetes. In our study, we found that ischemic heart disease, hypertension, presence of metabolic syndrome, atrial fibrillation, peripheral artery disease, obesity (BMI $\geq$ 30 kg/m^2) and renal impairment (GFR< 60 mL/min/1.73 m^2) are the factors statistically associated with new cases of heart failure. Age, duration of diabetes and use of insulin were not significantly associated with the presence of suspected new heart failure in our study group. Higher odds ratio and broader 95% CI obtained in our analysis as compared with other studies are explained by a weaker statistical power of our study group, which was originally designed only to determine the prevalence of HF in a cohort of patients with diabetes.

LIMITATIONS OF THE STUDY

The main limitation of the study was the use of ECG as the only objective sign of cardiac engagement and not chest X-ray, echocardiogram or natriuretic peptides, with the risk of false-positive diagnosis. Therefore, the results should be interpreted as a screening outcome that needs further confirmation of HF diagnosis. ❑

Conclusion

Presence of HF in our group of patients with diabetes is under-estimated when based on patients' history. The active screening for HF, using a simple and accessible protocol for a diabetes out-patient clinic, more than doubles the number of HF cases. This would allow to a larger number of patients to benefit from preventive strategies that might reduce HF-related deaths and hospitalization for exacerbation of HF episodes.

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