VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2014, Vol. 21, No. 3, pp. 265–272
DOI: 10.5603/CJ.a2013.0117

ISSN 1897–5593

Regional differences among female patients with heart failure from the Cardiac Insufficiency BIsoprolol Study in ELDerly (CIBIS-ELD)

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Abstract

Background: *The aim of our study was to examine regional differences in the demographics, etiology, risk factors, comorbidities and treatment of female patients with heart failure (HF) in the Cardiac Insufficiency BIsoprolol Study in ELDerly (CIBIS-ELD) clinical trial.*

Methods and results: *One hundred and fifty-nine female patients from Germany and 169 from Southeastern (SE) Europe (Serbia, Slovenia and Montenegro) were included in this sub-analysis of the CIBIS-ELD trial. Women comprised 54% of the study population in Germany and 29% in SE Europe. German patients were significantly older. The leading cause of HF was arterial hypertension in German patients, 71.7% of whom had a preserved ejection fraction. The leading etiology in SE Europe was the coronary artery disease; 67.6% of these patients had a reduced left ventricular ejection fraction (34.64 ± 7.75%). No significant differences were found in the prevalence of traditional cardiovascular risk factors between the two regions (hypertension, diabetes, hypercholesterolemia, smoking and family history of myocardial infarction). Depression, chronic obstructive pulmonary disease and malignancies were the comorbidities that were noted more frequently in the German patients, while the patients from SE Europe had a lower glomerular filtration rate. Compared with the German HF patients, the females in SE Europe received significantly more angiotensin converting enzyme inhibitors, loop diuretics and less frequently angiotensin receptor blockers and mineralocorticoid receptor antagonists.*

Conclusions: *Significant regional differences were noted in the etiology, comorbidities and treatment of female patients with HF despite similar risk factors. Such differences should be considered in the design and implementation of future clinical trials, especially as women remain underrepresented in large trial populations.* (Cardiol J 2014; 21, 3: 265–272)

Key words: heart failure, diastolic, systolic, female, clinical trial

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Received: 11.05.2013 Accepted: 03.08.2013

Introduction

Cardiovascular diseases are the main cause of mortality in the European Union, accounting for near 40% of deaths in the total population. Around 1–2% of the population in European countries suffers from heart failure (HF), with the prevalence rising to ≥ 10% among the population aged ≥ 70 years [1].

Underrepresentation of women in cardiovascular trials has been clearly demonstrated in the past. Since 2006, 11 randomized trials of HF have included 46,141 patients, 12,834 of whom were women (27.8%, range 15–60%).

In Europe women have a longer life expectancy with marked differences among different countries. This gender gap in life expectancy, favoring women, shows a threefold variation among the countries [2].

The past decade has seen a trend toward the globalization of clinical trials with greater participation of the emerging countries [3]. The balance among the regions represented in the trial is important in order to avoid over-representation and possible interpretation bias. Despite relatively strict inclusion and exclusion criteria in HF trials, patient populations remained heterogeneous among the regions in terms of baseline characteristics, treatment and outcomes. However, regional differences should not discourage the globalization of clinical trials; it is interesting to note that subgroup analyses based on geographical regions have rarely changed the main results of HF trials [4, 5].

Although women comprise 40% of the HF population, they are underrepresented in clinical trials [6]. Cardiovascular diseases are the leading cause of death in Europe among women, proportionally more than among men (54% vs. 43%). However, this is not reflected in current HF registries, which have a predominately male population from Western European countries. Furthermore, current guidelines do not include gender-related management recommendations.

Little is known about gender-related differences in HF patients in terms of clinical characteristics, echocardiographic measures and outcomes. Women more frequently have HF with preserved left ventricular (LV) function. They are also significantly older than male HF patients, probably due to the later onset of HF [7, 8].

The multinational, multicenter, prospective, randomized Cardiac Insufficiency BIsoprolol Study in ELDerly (CIBIS-ELD) study, which compared the short-term titration of bisoprolol and carvedilol in HF patients, lends itself particularly to the exploration of basic regional differences in an underrepresented population — elderly female patients with chronic HF from Germany and Southeastern (SE) Europe.

The aim of our study was to compare female populations with chronic HF from these two different regions focusing on the differences which could influence the design of future clinical trials and ultimately to the guidelines development.

Methods

CIBIS ELD is a double-blind superiority trial comparing the titration of bisoprolol vs. carvedilol in elderly patients suffering from HF with the reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF). Patients were 65 years old or older with the symptomatic chronic HF consistent with New York Heart Association (NYHA) functional class ≥ II at the time of inclusion or with LVEF ≤ 45%. At the beginning of the study, participants had to be beta-blocker naïve or on ≤ 25% of the guideline-recommended target or equivalent dose. The study participants had to be clinically stable and on stable medication for 2 weeks prior to randomization. Major exclusion criteria were: known contraindications to beta-blocker treatment, such as hypotension with a resting systolic blood pressure < 90 mm Hg, severe pulmonary disease or severe asthma, heart rate < 55/min prior to the commencement of the therapy, the second or third degree sinoatrial block (without pacemaker), and diagnosed sick sinus syndrome. Tolerability, defined as achieving guideline--recommended beta-blocker doses after 12 weeks, was assessed as the primary endpoint [9].

In this analysis based on the CIBIS-ELD study population we included 159 patients from Germany (54% of all the included patients from Germany) and 169 patients from SE Europe (29% of all the included patients from SE Europe). Female patients from Germany and SE Europe had different profiles of cardiovascular characteristics, co-morbidities, and risk factors.

Baseline variables were presented as frequencies and percentages for binary variables or means and standard deviations for quantitative variables. Comparisons of the groups were performed by the χ^2 test or analysis of variance, respectively. $P < 0.05$ was considered statistically significant. SPSS version 17 was used as statistical software.

Results

General characteristics

Baseline characteristics are presented in Table 1. Women from Germany were significantly older, with a shorter duration of HF. There was a significant difference in HF etiology observed between the two regions. HFpEF was the most common type in women from Germany (71.7%) compared to HFrEF in women from SE Europe (67.6%). In SE European patients with HFrEF the average LVEF was 34.64 ± 7.75%, while in the same subgroup of German female patients it was 35.74 ± 8.72%.

In the majority of patients dyspnea was reported on mild exertion (NYHA class II) (Fig. 1). However, there were significant differences in NYHA class distribution between the observed groups ($\chi^2 = 10.89$, $p < 0.05$). The patients in SE Europe were generally more symptomatic than the German patients. Similarly, female patients from SE Europe had significantly higher N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels at the beginning and at the end of the study (Table 1).

Risk factors

There were no significant differences in smoking habits (Fig. 2). Hyperlipidemia was similarly distributed in both regions (prevalence in Germany 67.9% vs. SE Europe 63.9%, p = 0.485; cholesterol level 5.54 ± 1.23 vs. 5.76 ± 1.56 mmol/L, p = 0.167). There were no significant differences in percentages of reported family history of fatal myocardial infarction (MI) before the age of 60 years (Germany and SE Europe: 20.1% vs. 15.4%, p = 0.164).

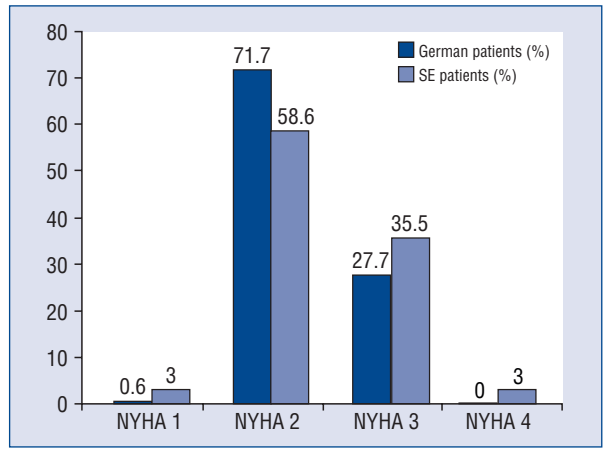

Figure 1. Distribution of functional New York Heart Association classes in patients from Germany and Southeastern Europe.

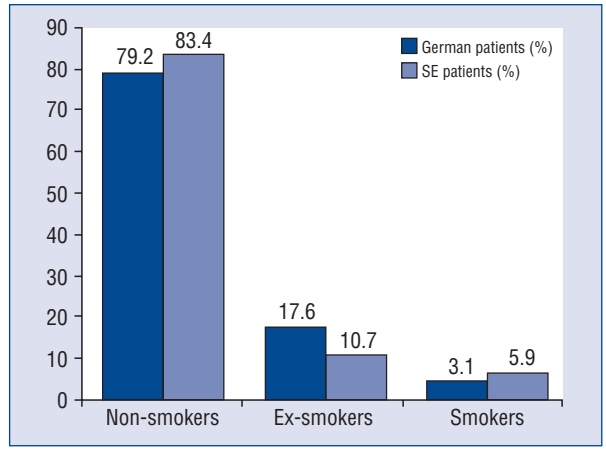

Figure 2. Smoking habits between German and patients from Southeastern Europe.

Table 1. Baseline patients' characteristics.

Patients' characteristics	Female patients from Germany	Female patients from SE Europe	P
Age [years]	74.13±6.16	72.20±4.84	< 0.01
Duration of HF [years]	1.49 ± 3.88	5.47 ± 6.17	< 0.001
Etiology of HF	AH: 65.2%	CAD: 46.3%	< 0.001
History of angina pectoris and MI	35.5%/15.1%	82.6%/17.4%	< 0.001/ /< 0.001
HFpEF	71.7%	32.4%	< 0.001
Atrial fibrillation	6.9%	16.6%	< 0.01
Pacemaker rhythm	3.1%	1.8%	< 0.05
Baseline NT-proBNP levels [pg/mL]	645.5 ± 1163.1	1560.5 ± 2242.9	< 0.001
Post-treatment NT-proBNP levels at the end of study [pg/mL]	673.8 ± 1162.04	1145.3 ± 469.5	< 0.01
Left ventricular ejection fraction	51.57 ± 14.8%	36.68 ± 9.6 %	< 0.001

AH — arterial hypertension; CAD — coronary artery disease; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; MI — myocardial infarction; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; SE — Southeastern

No difference was observed in the prevalence of arterial hypertension (Germany vs. SE Europe: 86.8% vs. 88.2%, p = 0.741), however there were significant differences in its severity. Women from SE Europe more commonly had mild hypertension (stage 2 according to ESC guidelines) in comparison to those from Germany, where stages 3 and 4 were more frequently observed (χ^2 = 13.5, p < 0.01) [10].

Women from Germany were more commonly obese than those from SE Europe (body mass index [BMI]: 30.3 ± 6.5 vs. 27.7 ± 4.9, F = 16.675, p < 0.001).

Alcohol consumption was different between the observed groups: χ^2 = 29.86, p < 0.01. Only 10.7% of the SE European patients reported alcohol consumption compared to 29.1% of the German patients. The majority of the German patients consumed only 1 drink per week defined as 0.25 L of beer or 0.1 L of wine or 2 cl liquor.

Hyperuricemia was more prevalent among the patients from Germany: 15.1% vs. 2.4%, χ^2 = 16.99, p < 0.001.

Comorbidities

No significant differences were observed in the prevalence of diabetes, cerebrovascular morbidity, anemia (hemoglobin levels: 13.25 ± 1.44 vs. 12.97 ± ± 1.44 mg/dL, p = 0.08) and renal diseases (Fig. 3) between the female patients from Germany and those from SE Europe.

However, despite similar rates of previously known renal diseases (diagnosed and treated by nephrologists), we found significant differences in creatinine values (Germany: 83.74 ± 28.93 μmol/L vs. SE Europe: 95.37 ± 34.2 μmol/L, p < 0.001) and concurrent glomerular filtration rate (GFR) calculated with Modification of Diet in Renal Disease formula (Germany: 68.22 ± 26.88 mL/min vs. SE Europe: 57.98 ± 20.63 mL/min, p < 0.001) [11].

Women from Germany more frequently had the chronic obstructive pulmonary disease (COPD) (10.1% vs. 2.4%, χ^2 = 8.5, p < 0.01), depression (18.9% vs. 4.1%, χ^2 = 17.75, p < 0.001) and malignant diseases (13.8% vs. 1.2%, p < 0.0001).

Socio-economic characteristics and the use of medical services

There was a considerable diversity regarding patients' level of education, but in general, those from Germany had a higher education level. More patients from SE Europe reported not having any education (14.1% vs. 4.2%, p < 0.001). There were significantly more patients with only primary education in Germany (32.5% vs. 19.5%, p < 0.01), while more patients from SE Europe reported having finished the secondary school (28.9% vs. 15%, p < 0.01). Twenty-six German patients and only 6 from SE Europe had university degrees (p < 0.001).

Women from SE Europe more frequently visited the cardiologist during 1 year (Table 2).

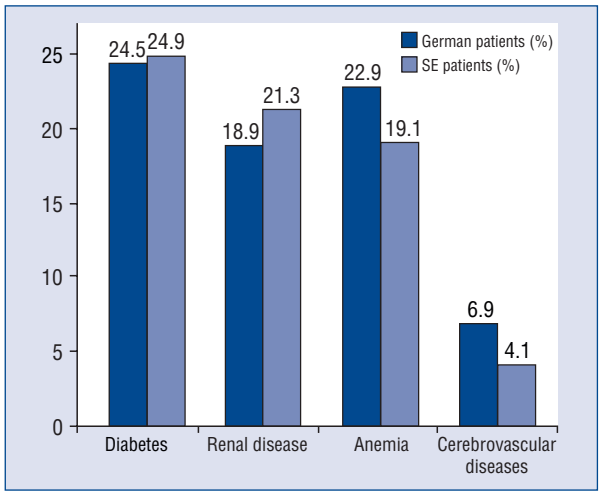

Figure 3. Co-morbidities in female German and patients from Southeastern Europe.

Heart failure therapy and concomitant medication

Significant differences were noted in the HF therapy in the observed patients (Table 3). Prior to the inclusion in the study more women from SE Europe were taking beta-blockers (66.3% vs. 40.3%, p < 0.001). Similar results for beta-blocker therapy were observed for the subgroup of patients with the diastolic dysfunction (SE Europe and Germany: 76.9% vs. 37.7%). There were also differences in the type of the prescribed beta-blocker. Female patients from Germany most frequently used the selective $beta_1$ receptor blocker metoprolol 51.6%, while women from SE Europe were prescribed most frequently the nonselective $beta/alpha_1$ blocker carvedilol 39.6% (p < 0.001).

Patients from SE Europe more frequently had angiotensin converting enzyme (ACE) inhibitors, acetylsalicylic acid, organic nitrates, oral anticoagulants, antiarrhythmic agents and loop diuretics and less frequently angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRAs), antidepressants and allopurinol. No difference was observed regarding the device and surgical therapy for cardiovascular diseases (Table 4).

Table 2. Number of contacts with health care professionals in patients from Germany and Southeastern (SE) Europe.

Number of contact with health care professionals during 1 year	Patients from Germany	Patients from SE Europe	P
Number of visits to cardiologist during 1 year	2.9 ± 1.9	0.67 ± 1.2	< 0.001
Number of visits to primary care physician during 1 year	6.2 ± 5.9	6.67 ± 4.2	0.409
Number of hospitalizations during 1 year due to worsening heart failure	0.31 ± 0.73	0.44 ± 0.63	0.951
Number of hospitalizations in rehabilitation facilities during 1 year due to heart failure	0.06 ± 0.25	0.06 ± 0.28	0.82

Table 3. Therapy in patients from Germany and Southeastern (SE) Europe.

Drug	Germany patients (n = 159)	SE Europe patients (n = 169)	P	Germany patients with HFpEF (n = 114)	SE Europe with HFpEF (n = 55)	P
ACEI/ARB	50.9%	85.2%	NS	29.8%	3.8%	< 0.05
Loop diuretics	27%	46.7%	< 0.001	23.7%	19.2%	NS
Thiazide diuretics	33.3%	27.8%	NS	38.6%	53.8%	NS
Mineralocorticoid receptor antagonists	36.1%	6.9%	< 0.001	1.8%	15.4%	< 0.05
Digitalis	7.5%	10.1%	NS	2.6%	7.7%	NS
Organic nitrates	6.9%	39.1%	< 0.001	6.1%	23.1%	< 0.05
Calcium channel blockers	18.4%	23.7%	NS	21.2%	46.2%	< 0.05
Antiarrhythmics	0.6%	11.2%	< 0.001	0.9%	3.8%	NS
Statins	28.9%	39.1%	0.053	26.3%	30.8%	NS
Other lipid lowering agents	1.3%	1.2%	NS	1.8%	0%	NS
Acetylsalicylic acid	41.5%	68.6%	< 0.001	36.8%	65.4%	< 0.001
Other antiplatelet therapy	5.7%	5.3%	NS	1.5%	0%	NS
Oral anticoagulants — vitamin K antagonists	10.1%	18.9%	< 0.05	7%	7.7%	NS
Other oral anticoagulants	1.3%	1.8%	NS	0.9%	0.0%	NS
Antidepressants	7.5%	1.2%	< 0.01	7%	3.8%	NS
Allopurinol	6.9%	0.0%	< 0.001	78.6%	0.0%	< 0.001

ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; HFpEF — heart failure with preserved ejection fraction

Table 4. Device therapy or cardiovascular surgery in patients from Germany and Southeastern (SE) Europe.

Device or surgical therapy	Germany patients (n = 159)	SE Europe patients (n = 169)	P
Valvular replacement	3.1%	3.6%	NS
Coronary artery bypass graft	3.1%	8.9%	0.058
Percutaneous coronary intervention	11.3%	5.9%	NS
Pacemaker	4.4%	3%	NS
Cardiac resynchronization therapy	1.3%	0%	NS
Implantable cardioverter-defibrillator	0.6%	0%	NS

Discussion

Female population was underrepresented in SE Europe considering that in both regions patients were recruited in consecutive order during their regular visits to a cardiologist.

Our results showed marked differences in the etiology and treatment of HF in elderly female population from different parts of Europe.

In Germany, arterial hypertension was the most common cause of HF in women, while in SE Europe it was the coronary heart disease (CHD). No regional differences in the prevalence of arterial hypertension were found in this study (but it was more severe in female patients from Germany), although the data from the EVEREST study suggest that it is more prevalent in Eastern Europe [12].

Women from SE Europe develop HF earlier than German women, which could be attributed to coronary events which occurred at the younger age [5]. These results are in accordance with the higher rates of MI in Eastern Europe reported in a series of studies, where it was attributed partly to socioeconomic factors — lower education in women and lower income, emotional stress, unhealthy dietary style, and less physical activity as the most prominent but not all the factors [13]. The rates of MI in women correlate closely with the reported rates in men in different parts of Europe, suggesting also that the environmental and lifestyle factors have significant influence on CHD development beside the "traditional risk factors" — genetics and gender [14].

Our female patients had similar cardiovascular risk factors with several key differences. In contrast to the previously published data that smoking-related mortality is higher in Eastern European countries [15], we found no significant regional differences in tobacco use. This could be attributed to the fact that we observed only elderly female population. German patients more frequently consumed alcohol but moderately (1 drink per week), which is consistent with previous studies of alcohol consumption in women with higher education and socio-economic status. Furthermore, moderate alcohol intake may have a protective effect against CHD [16, 17].

German patients had a higher average BMI and were more frequently diagnosed with hyperuricemia. Recent data indicate, however, that Eastern European countries have the highest obesity prevalence rates for both genders, which is explained by a transition in the social, economic, and nutritional environments followed by the delayed effect of the Western lifestyle in the countries of the former "Eastern Bloc" [18–20].

Differences in BMI seen in this study could be due to HF duration, because HF has inflammatory components and leads to a progressive weight loss over time. The females from SE Europe had a longer history of HF and hence they had more complications of the disease itself, including the weight loss.

In SE Europe patients NT-proBNP levels were higher. Because measurements of NT-proBNP levels are useful in both diagnosis and prognosis in patients with chronic HF [21], this finding could suggest either more clinically severe HF or the undertreatment with poorer subsequent prognoses in SE Europe patients.

HF patients usually have 1 or more comorbidities, which are complications of HF or the combination of HF, its underlying etiology and advanced age [22]. Similarly, our patients had a high prevalence of anemia and diabetes. However, there was no significant differences between the regions. Previous studies reported higher prevalence of chronic kidney diseases in Western Europe [12], although in our study patients from SE Europe had lower GFR, which could be attributed to longer disease duration, more severe forms of HF in those patients and, possibly, the applied therapy. Interestingly, higher NT-proBNP levels could be attributed not only to lower LVEF but also to the lower GFR in SE Europe patients [23].

As previously described, we also found regional differences in the prevalence of COPD [12]. German patients had more frequently COPD, which could be attributed in our study population to more frequent obesity in these patients [24]. Primary pulmonary hypertension was rare, while secondary pulmonary hypertension is a common feature of HF and it is associated with high morbidity and mortality [25, 26].

The patients from SE Europe more frequently had atrial fibrillation, which could be attributed to a higher prevalence of HFrEF and valvular disease [27].

The female patients from Germany more frequently had malignant diseases, which are more prevalent in developed, high income countries; regional variation has been attributed to different lifestyle and environmental factors [28]. In our study, females from SE Europe had less frequent depression and less frequently took antidepressants than those living in Germany, which is not in accordance with previous publications [29].

We found marked differences in the socioeconomic composition of the German and SE European study populations, which could have relevant impact

on health care use and outcomes. Although most health professionals may see CHD merely as a problem of the individual, socioeconomic factors are key determinants of CHD and its related risk factors. Both health care and schooling are in the group of socioeconomic factors, which could act next to the traditional risk factors [14]. While the control of traditional risk factors is not incompatible with strategies at the societal level, in order to effectively reduce cardiovascular mortality in both developed and developing societies, a broader socioeconomic approach is needed. German participants were more likely to have a university degree. Also, the pension system in Western Europe provides significantly higher monthly payment than those from SE Europe. More frequent visits to cardiologists in SE European countries could be ascribed to a more direct contact, which does not require always a referral from the patient's primary care physician.

Different drugs were used in the observed groups of patients, which is in accordance with previous trials, in which different therapeutic approaches in HFpEF and HFrEF were investigated [30]. Since patients from SE Europe more frequently had CHD, they more frequently used organic nitrates, antiarrhythmics, platelet aggregation inhibitors and anticoagulant therapy. Loop diuretics were more frequently used in patients with HFrEF from SE Europe, as well as ACE inhibitors (in both HFrEF and HFpEF patients). German patients more frequently used ARBs. Although digitalis is used to manage symptoms of HF it was not used more frequently in patients with HFrEF. In German patients MRAs were more frequently used, however in the subgroup of SE Europe patients with HFpEF those drugs were more frequently prescribed. More women from SE Europe were taking beta-blockers prior to inclusion in the study, which could be attributed to a higher rate of coronary artery disease in SE Europe. Similar results were observed for the subgroup of patients with the diastolic dysfunction. There were also differences in the type of prescribed beta-blocker. Female patients from Germany most frequently took the selective $beta_1$ receptor blocker which could be attributed to more frequent COPD.

Limitations of the study

All patients took part in a controlled, randomized trial with strict inclusion and exclusion criteria and different recruitment methods, therefore obtained results are not representative of the German and SE European population.

Conclusions

We found significant regional differences in female HF patients regarding the etiology, comorbidities and treatment. No significant differences were observed in the prevalence of traditional cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking and family history of MI). Female population from SE Europe was underrepresented (29% of all participants) in comparison to those from Germany (54% of the study population). Taking into the consideration that this was a trial with strict inclusion/exclusion criteria, and our recruitment method was similar we could speculate that females from SE Europe could have less frequent HF, under-diagnosed HF, higher mortality from CHD and less odds to develop HF, but the end-result is decisively the same — female patients from SE Europe were underrepresented in the trial.

The current guidelines on HF from ESC and other cardiology societies do not include specific gender-related issues, except in the case of pregnancy. No regional differences are even considered. All the mentioned differences should be considered in the design and implementation of future clinical trials, especially as women have been underrepresented in large trial populations for the past few decades. Furthermore, not only the women but elderly have often been either excluded or underrepresented in cardiovascular trials, and as such the evidence base is rather unsatisfactorily drawn either from the observational cohorts or from small numbers within larger randomized trials.

There is a need that cardiovascular trials incorporate sufficient number of patients with different gender, age, and ethnicity to provide better insights in disease etiopathology, diagnosis and treatment.

Acknowledgements

This study was supported by the German Competence Network Heart Failure, funded by the Federal Ministry of Education and Research (BMBF), FKZ 01GI0205.

Conflict of interest: none declared

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