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Geographical differences in heart failure characteristics and treatment across Europe: results from the BIOSTAT-CHF study

Carlo Lombardi, MD¹ João Pedro Ferreira, MD, PhD²; Valentina Carubelli, MD¹; Stefan D. Anker, MD, PhD³; John G. Cleland, MD, PhD⁴; Kenneth Dickstein, MD, PhD^{5,6}; Gerasimos Filippatos, MD, PhD⁷; Chim C. Lang, MD⁸; Leong Ng, MD⁹; Piotr Ponikowski, MD, PhD¹⁰; Niles J. Samani, MD, PhD¹¹; Dirk J. van Veldhuisen, MD, PhD¹²; Faiez Zannad, MD, PhD²; Adriaan Voors, MD, PhD¹²; Marco Metra, MD¹

Affiliations:

¹ Cardiology, Department of Medical and Surgical Specialties, radiological Sciences and Public Health. University of Brescia. Italy

² INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Université de Lorraine, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France.

³ Department of Innovative Clinical Trials, University Medical Centre Göttingen (UMG), Robert-Koch-Straße, D-37075, Göttingen, Germany.

⁴ Robertson Centre for Biostatistics and Glasgow Clinical Trials Unit, Glasgow, UK.

⁵ University of Bergen, Bergen, Norway.

⁶ Stavanger University Hospital, Stavanger, Norway.

⁷ National and Kapodistrian University of Athens, School of Medicine, Heart Failure Unit, Department of Cardiology, Athens University Hospital Attikon, Rimini 1, Athens 12462, Greece.

⁸ Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.

⁹ Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, United Kingdom

¹⁰ Department of Cardiology, Centre for Heart Diseases, 4th Military Hospital, Wroclaw, Poland; Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland.

¹¹ Department of Cardiovascular Sciences, University of Leicester, BHF Cardiovascular Research Centre, Glenfield Hospital, Groby Rd, Leicester, LE3 9QP, United Kingdom

¹² Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

Short running title: Geographical differences in the BIOSTAT-CHF study

Word count: 4137

Key words: heart failure; geographical variations; geographical differences; income; outcomes; BIOSTAT-CHF

Corresponding author

Marco Metra, MD. Division of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University and Civil Hospital of Brescia, Brescia, Italy.

Abstract (187 words)

Background: Geographical differences may impact treatment of heart failure (HF) and the results of clinical trials. We have investigated differences between geographical areas across Europe in the BIOSTAT-CHF program.

Methods: Patients with worsening HF enrolled in BIOSTAT-CHF were subdivided, according to the European geographical areas, into those from Northern countries (NC, Netherlands, Norway, Sweden, United Kingdom), Central countries (CC, Germany, Poland, Serbia, Slovenia), and Mediterranean countries (MC, France, Greece, Italy). Patients were compared for baseline characteristics, treatment, and outcomes. The primary endpoint was a composite of all-cause mortality or HF hospitalization.

Results: Among 2516 patients enrolled in BIOSTAT-CHF, 814 (32.3%) were from NC, 816 (32.4%) from CC, and 886 (35.2%) from MC. Patients from NC were older, had more severe signs and symptoms of HF and non-cardiac comorbidities, compared to those from CC and MC. The primary endpoint occurred at a higher rate in NC (44.3% versus 37.4% in CC and 39.6% in MC; $p=0.014$) but this difference became non significant after adjustment for baseline variables.

Conclusion: Several differences in patients' profile and treatment were identified across Europe in BIOSTAT-CHF and they accounted for differences in outcomes.

Key-words: geographical differences; heart failure; treatment up-titration.

Opmerking [VA(1): If possible (in terms of word count) I would advise not to abbreviate NC, CC, and MC. (just a matter of taste)

Opmerking [VA(2): Please specify which co-morbidities. In the discussion you seem to write the opposite i.e. lower prevalence of co-morbidities in Northern Countries

Introduction

Heart failure (HF) has a worldwide diffusion and its prevalence is increasing due to the aging of the population and the efficacy of treatment of acute cardiovascular diseases.^{1,2,3,4} Geographical differences may have an impact on clinical characteristics and treatment of the patients with HF and influence the results of clinical trials.^{5,6,7,8,9} These differences may be important even within one single continent, such is the case of European countries.^{10,11,12,13} This was first shown in retrospective analyses of randomized trials and then in registries.^{14,15,16} The European Society of Cardiology (ESC) HF Pilot Survey showed differences across European geographical areas.¹⁵ Patients from Eastern European countries were younger, with a more frequent ischemic etiology and had higher systolic blood pressure. Patients in Northern countries had a lower left ventricular ejection fraction (EF). Devices were underused in Eastern countries.¹⁵ In the more recent ESC-HF Long-term registry, patients from middle Eastern and Northern European countries were older and more likely to have an ischemic etiology. The use of implantable cardioverter defibrillators (ICDs) or cardiac resynchronization therapy with defibrillation (CRT-D) was also different across European areas. Geographical areas were independently related with outcomes of chronic heart failure patients at multivariable analysis, with a lower risk of events in Northern European versus Southern European countries.^{16,17}

The BIOlogy Study to Tailored Treatment in Chronic HF (BIOSTAT-CHF) is a European multicenter, prospective study which included patients with worsening signs and/or symptoms of HF who were considered to be on suboptimal medical treatment.¹⁸ Patients were enrolled from 11 European countries. This study therefore allows the assessment of geographical differences between different areas of Europe with respect of a peculiar study population, that is to say patients with worsening HF followed by mostly tertiary referral centers. The aim of this secondary, non-prespecified, analysis is to investigate the geographic differences in the clinical characteristics,

prognosis, and treatment between the patients enrolled from different geographical areas in BIOSTAT-CHF.

Methods

The design and main results of the study is described in detail elsewhere.¹⁸ In summary eligibility criteria at screening included signs and symptoms of new-onset or worsening HF, cardiac dysfunction shown by a left ventricular EF $\leq 40\%$ or brain natriuretic peptide (BNP) >400 pg/mL or N-terminal pro-brain natriuretic peptide (NT-proBNP) >2000 pg/mL, treatment with oral or intravenous furosemide or equivalent ≥ 40 mg daily. Patients had to be not previously treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs) and beta-blockers or should have been receiving $\leq 50\%$ of their target doses according to current guidelines.¹⁹

Patients hospitalized for acute HF and outpatients with of signs and symptoms of HF could be included in the study. The primary endpoint was time to a composite of all-cause death and heart failure hospitalization. The trial was approved by the ethics committee at each study center. All the patients provided written informed consent. The study design included a 3-month uptitration phase, during which the investigators had to introduce and/or uptitrate guidelines-recommended medications with special attention to ACE-inhibitors, ARBs, beta-blockers and mineralocorticoid receptor antagonists (MRA). The NT-proBNP values were measured using the Proseek Multiplex are CVDIII panel (Olink Proteomics AB, Uppsala, Sweden) and presented in normalized protein expression (NPX) values, which is an arbitrary unit on a log2 scale in which a high value corresponds to a higher protein expression.²⁰

Opmerking [VA(3): Please add: [Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure.](#)

Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Ng LL, Metra M, Ter Maaten JM, Lang CC, Hillege HL, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD, Zwinderman AH. Eur J Heart Fail. 2017 May;19(5):627-634.

[Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study.](#)

Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH. Eur Heart J. 2017 Jun 21;38(24):1883-1890.

[Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF.](#)

Ferreira JP, Rossignol P, Machuga JL, Sharma A, Gierd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, Ter Maaten JM, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A, Zannad F. Eur J Heart Fail. 2017 Oct;19(10):1284-1293.

For the purpose of this analysis, the study patients of BIOSTAT-CHF were subdivided according to their country of origin geographical areas. Northern countries included Netherlands, Norway, Sweden, and United Kingdom; Central countries included Germany, Poland, Serbia, and Slovenia; Mediterranean countries included France, Greece, and Italy.

Statistical Analysis

Continuous variables are shown as mean $\pm$ standard deviation, dichotomous variables as number (%). Comparisons of demographic and clinical baseline characteristics, medical history, and medications were evaluated by ANOVA for continuous variables and the χ^2 test for categorical variables. Categorical variables are expressed as frequencies and proportions (%). Individual country contribute to enrollment and treatment according to geographic area are expressed as frequencies and proportions (%). Kaplan Meier plots were generated by each area to evaluate clinical outcomes. A p value <0.05 was used to indicate statistical significance. The outcomes of interest are time to a composite of death or unscheduled hospitalizations for heart failure, HF hospitalization, and all-cause mortality. Cox proportional hazard regression models were used to model long-term event rate both in univariable and multivariable analysis. A validated multivariable risk model was used to predict all-cause mortality and hospitalizations and assess the independent prognostic value of geographical areas.²¹ Cox model's assumptions has been verified. Statistical analysis was performed with Stata[®] software 14.2 (Release 14, 2015, StataCorp LP, College Station, Texas), was used for the main analysis.

Results

Patients were enrolled from December 2010 to December 15th 2012. The end of study follow-up was on April 1st 2015. A total of 2516 patients were enrolled in the BIOSTAT-CHF study with a median follow-up of 21 months (interquartile range, 15–27 months). The distribution according to the geographic region was as follows: 814 (32.3%) in Northern countries, 816 (32.4%) in Central countries, and 886 (35.2%) in Mediterranean countries. Results regarding baseline characteristics of the patients subdivided according to the European area are shown in **Table 1** and individual country contribute to enrollment in the study is represented in figure 1. Data about enrollment contribute and baseline characteristics for each individual country are listed in **Table 2**.

Baseline characteristics

Patients from Northern European countries were older, more often female, had higher heart rate (88.3 ± 24.7 beats per minute in Northern area vs 79.6 ± 19.5 Central area and 79.3 ± 18.4 in the Mediterranean area; $p < 0.001$), more severe signs and symptoms of HF and higher NT pro BNP values (3.40 ± 1.34 pg/mL in the Northern area vs 2.79 ± 1.39 pg/mL in the Central area vs 2.89 ± 1.36 pg/mL in the Mediterranean area; $p < 0.001$). Glomerular filtration rate was lower in Northern area patients compared with others (eGFR, mL/min/1.73m², NC 58.9 ± 23.0 , CC 66.3 ± 22.4 , MC 62.2 ± 23.6 , $p < 0.001$).

Figure 4 represents the country-by-country distribution of signs of congestion. Patients from the Northern European countries tended to have a higher prevalence of pulmonary congestion, peripheral edema and elevated jugular venus pressure.

Patients from Central Europe were the younger (66.1 ± 10.7 years, $p > 0.001$), with a numerical higher prevalence of ischemic etiology of HF (46.7% versus 39.9% in Northern countries versus 45.7% in Mediterranean countries) and with higher prevalence of hypertension ($p = 0.038$), whereas the proportion of patients with atrial fibrillation was numerically lower compared with

Opmerking [c4]: I have not understand how describe this data
These should be units ("NPX") please ask Wouter or Jasper

other areas (41.8% versus 47.5 Northern area versus 46.8% Mediterranean area **Table 1**). The use of implantable devices were most common in Mediterranean countries as well a previous history of coronary revascularization with percutaneous coronary angioplasty (PCI) or coronary artery by-pass (BPAC).

Opmerking [VA(5)]: Please do not use this abbreviation.

Treatment

Data regarding treatments are shown in Table 1 and Figure 2 and refer to the end of the 3-months uptitration period. The prescription of guidelines-recommended therapies varied widely across groups. Patients from Central Europe received more ACE-inhibitors or ARBs compared to those from Northern European and Mediterranean countries (78.4% versus 73.3% and 63.6%, respectively). Even beta-blockers and MRA were administered more often in central Europe compared with the other countries (87.5% versus 81.3% and 80% for beta-blockers and 66.5% versus 42.6% and 50.7% in Northern European and Mediterranean countries, respectively).

Digoxin was still frequently prescribed in Central Europe (23.5%) and was relatively uncommon in Mediterranean patients (14.6%). Loop diuretics were prescribed in almost all patients, with slightly lower, but statistically significant ($p=0.026$), rates in Mediterranean countries (99.1% versus 99.5% and 100% in the Northern and Central countries, respectively).

Opmerking [VA(6)]: Please note that this was required by the protocol!

Opmerking [c7]: Dr.Woors: First, I was afraid about duplicate data on uptitration of therapy, since it was already described in the paper by Wouter that you had attached. However, strictly speaking, we did not report on the differences on medication use and uptitration in the three regions. So, we cannot be blamed by publishing duplicate findings. We might suggest to still have this in the paper, albeit not too much pronounced. What do you think?
Dr.Metra: Yes. We show the data for the 3 groups and we take care if this in the discussion

Notably, the proportion of patients receiving $\geq 50\%$ of the target dose of both ACE-I/ARB after the uptitration phase was higher in the Northern countries compared with the other regions (60%, versus 58.7% in the Central countries and 46.5% in the Mediterranean ones; $p=0.001$). Similarly, achievement of $\geq 50\%$ of the target doses of beta-blockers was greater in patients in the

I briefly include in the results and also in the discussion the data on uptitration of therapy in the 3 regions

Northern countries than in the Central and Mediterranean ones (46.6%, 32.5%, 31.2%, respectively, $p < 0.001$).

Outcomes and interaction with treatment

The incidence of the endpoints and the prognostic models are shown in **Table 1**. Patients from Central countries had the numerical lower rate of the primary endpoint of the study of all-cause mortality and HF hospitalization (44.3% in the Northern countries versus 37.4% in the Central countries and 39.6% in the Mediterranean ones; $p=0.014$). A similar result was found for all-cause mortality (29.2%, 24.1% and 25.1% in the Northern, Central and Mediterranean countries, respectively; $p=0.043$) and HF hospitalizations alone (27.1%, 21.0% and 24.5% in the Northern, Central and Mediterranean countries, respectively; $p=0.014$). During the uptitration period patients from Northern Europe had a significant increase in all-cause mortality compared with other regions (NC 8.2%, CC 5.3%, MC 4.6%, $p=0.004$). Figure 5 represents the country-by-country distribution of outcomes.

Unadjusted and adjusted outcome analyses for the primary and secondary endpoints are shown at **Table 3**. After adjustment for other predictors of outcome, there were no significant differences between geographical areas in terms of relative risk of clinical outcomes. Differences in the outcomes were evaluated by the Log-rank test and are shown in the Kaplan-Meier curves (figure 3A, 3B, 3C).

Discussion

This analysis of BIOSTAT-CHF shows that there are marked differences in patient characteristics and HF treatment in different geographical areas in Europe. Patients from Northern Europe were older, more often female and had higher heart rate, more severe signs and symptoms of HF and higher NT-proBNP values. Patients from Central Europe were younger, had a higher prevalence of hypertension and were more likely to receive ACE-inhibitor/ARBs, beta-blockers and MRAs at baseline. Mediterranean patients were more likely to be diabetics and had a greater history of PCA or CABG. A device implantation was more likely in these patients. In general, patients from Northern and Central Europe had a greater severity of heart failure (figure 4). These characteristics accounted for their worse outcomes so that differences in outcomes became not significant after adjustment at multivariable analysis.

In a previous analysis of BIOSTAT-CHF study reaching less of 50% of the recommended doses of ACE inhibitors/ARBs and beta-blockers was associated with a greater risk of death and/or heart failure hospitalization. The authors also demonstrated that achieving $\geq 50\%$ of the target doses of these drugs predicted better outcomes and this association persisted after adjustment for baseline variables.^{21,20,22} In our analysis patients from Northern Europe have reached higher doses of ACE-inhibitors/ARBs and beta-blockers compared with other regions. Patients from this region also showed at univariate analysis higher mortality rates during the titration period compared with Central and Mediterranean patients (table 1). Although patients from Northern Europe were the oldest, the presence of common co-morbidities usually related with age such as diabetes, arterial hypertension and chronic kidney disease were lower than in Central Europe and in the Mediterranean area. This data are also consistent with the Heart Failure Long-Term Registry (ESC-HF-LT) in which the proportion of patients with diabetes and hypertension in both acute and chronic HF were higher in the Northern Europe compared with other European countries.

Opmerking [c8]: Dr.Voors I think that the finding of a lower % of diabetes in the northern European countries is remarkable, in particular since they are much older, and one would expect higher % of diabetes based on the age differences. Do we have any explanation? To date, I don't but it's quite a difference and it has to be at least shown in the discussion. Carlo: Data regarding diabetes are consistent with other registries

AV: any difference in BMI?

Opmerking [VA(9)]: This is in contrast to what is stated in the abstract!!

In general our results confirm previous studies showing significant differences in the characteristics, outcomes and medical treatment of patients with HF from different geographical areas.⁵⁻¹⁴ Many factors may account for these differences within one continent and may include climate, socioeconomic conditions, income, health system organization. The organization of the health care system seems particularly important and may account for the greater severity of the patients followed in Northern European countries.²³ An intensive nurse-coordinated post-discharge program including nurse training to early recognize signs and symptoms of HF and telephone calls has been shown to improve outcomes, compared with standard usual care.²⁴ Non-pharmacological treatment of HF also differed across regions. Patients from the Central countries were less likely to receive ICD and CRT-D devices (compared with?) as well as coronary revascularization despite their higher proportion of coronary artery disease. Socioeconomic factors are well known determinants of the use of devices and may have had a major role also in our patients.²²

National income is another determinant of the quality of health care offered by a nation. Indeed, high income European countries provide citizens a better quality of care especially for what concerns disease-management specific programs as well as integrated prevention initiatives often realized with the help of dedicated medical and nurse-led programs.²⁵ The Prospective Urban Rural Epidemiologic (PURE) study has shown that the rates of major cardiovascular disease and death were higher in low-income countries than in high-income countries despite having a higher burden of cardiovascular risk factors.²⁶ The PURE study evaluated 628 urban and rural communities in 17 countries from Asia, Africa, North and South America and Europe.

Our results show the same events rates in patients coming from different countries, independently from their incomes. This may be caused by lower differences in the healthcare systems, above all when related to tertiary care centers, such as those involved in BIOSTAT-CHF,

compared to a worldwide study such as PURE. Income should, however, be considered as a potential novel variable on HF outcomes in the contest of international mega trials.^{27,28}

In our study, variables related to HF severity were the only determinants of outcomes at multivariable analysis. Medical treatment, despite significant geographical differences, had no independent role. This is likely caused by the importance of guidelines application in our study.

Limitations

One major limitation is the representativeness of our patients. BIOSTAT-CHF involved only 11 countries, so that a large number of European countries were not included. Even more important, only a few centers were included in each country and these were mainly tertiary care centers. The value of this analysis is more in showing how differences in clinical characteristics and medical prescriptions can lose their impact on outcomes once treatment is optimized in all the patients. The subdivision of countries was based on geographical criteria. However, this may not reflect real differences between different areas. For instance, the Mediterranean area was slightly penalized as represented only by two countries (Italy and Greece) with a strong Mediterranean vocation and by France, which has many social and economic aspects more closely related to the European Central countries. Differences in the health care systems, delivery of care and incomes are present between different geographical areas and they were likely the main determinants of our results. However, unfortunately these variables were not collected in BIOSTAT-CHF. Dietary aspects, such as salt content, may also have had a role.²⁶

However, all the countries in this study were broadly distributed across European territory and well represented each macro area. However, some sites have contributed to enrollment for a preponderant portion of patients for their respective country, and therefore a “single-center” driven effect cannot be excluded (supplementary table 1).

Conclusion

Several differences in patients' profile, treatment, and outcomes across Europe were identified in the BIOSTAT-CHF study. Despite the different clinical characteristics linked to the geographical area there were no differences in their outcomes after adjustment for baseline characteristics and treatment. Country incomes and healthcare organization might explain most of these differences.

Table legend

Table 1: baseline characteristics of the patients subdivided according to the European area

Variables	Northern Area	Central Area	Mediterranean Area	p value for trend
Number (%)	814 (32.3)	816 (32.4)	886 (35.2)	<0.001
Age, y	70.7±11.9	66.1±10.7	68.4±12.6	<0.001
Male sex, n (%)	548 (67.3)	624 (76.5)	674 (76.1)	<0.001
Race, n (%)				0.057
White Caucasian	802 (98.5)	813 (99.6)	874 (98.6)	
Other	12 (1.5)	3 (0.4)	12 (1.4)	
BMI, Kg/m ²	27.7±5.9	28.3±5.1	27.6±5.4	0.021
HR, bpm	88.3±24.7	79.6±19.5	79.3±18.4	<0.001
SBP, mmHg	125.3±24.8	126.4±19.8	122.6±20.7	0.001
Pulmonary rales, n (%)	434 (57.0)	364 (44.9)	493 (56.5)	<0.001
Peripheral edema, n (%)	455 (65.8)	415 (55.2)	386 (58.9)	<0.001
Elevated JVP, n (%)	249 (40.8)	128 (20.6)	177 (34.0)	<0.001
NYHA class III/IV, n (%)	506 (66.7)	492 (60.3)	524 (60.2)	0.010
Orthopnea, n (%)	370 (45.6)	238 (29.2)	271 (30.6)	<0.001
LVEF, %	31.6±11.9	30.7±10.8	30.8±9.3	0.280
Primary HF etiology, n (%)				0.006
Ischemic	317 (38.9)	381 (46.7)	405 (45.7)	
Hypertensive	79 (9.7)	89 (10.9)	86 (9.7)	
Valvular	72 (8.8)	63 (7.7)	55 (6.2)	
Other/miscellaneous	346 (42.5)	283 (34.7)	340 (38.4)	
Hemoglobin, g/dL	13.0±2.0	13.5±1.8	13.0±1.8	<0.001
eGFR, ml/min/1.73m ²	58.9±23.0	66.3±22.4	62.2±23.6	<0.001
Sodium, mmol/L	138.9±4.0	139.8±3.8	138.8±4.1	<0.001
Potassium, mmol/L	4.2±0.5	4.4±0.6	4.2±0.6	<0.001
LogNt-proBNP, ng/L	3.40±1.34	2.79±1.39	2.89±1.36	<0.001
Hypertension, n (%)	410 (50.4)	615 (75.4)	544 (61.4)	<0.001
Atrial Fibrillation, n (%)	387 (47.5)	347 (41.8)	415 (46.8)	0.038
Diabetes mellitus, n (%)	216 (26.5)	280 (34.3)	323 (36.5)	<0.001
COPD, n (%)	155 (19.0)	114 (14.0)	167 (18.8)	0.009
Stroke, n (%)	84 (10.3)	67 (8.2)	82 (9.3)	0.340
PAD, n (%)	81 (10.0)	78 (9.6)	114 (12.9)	0.055
Device therapy, n (%)	166 (20.4)	173 (21.2)	279 (31.5)	<0.001
PCI or CABG, n (%)	259 (31.8)	258 (31.6)	325 (36.7)	0.042
Loop diuretic, n (%)	810 (99.5)	816 (100)	878 (99.1)	0.026
ACEi/ARB, n (%)	597 (73.3)	640 (78.4)	583 (65.8)	<0.001
≥50% dose, n (%)*	389 (60.0)	422 (58.7)	359 (46.5)	0.001
Beta-blocker, n (%)	659 (81.0)	714 (87.5)	720 (81.3)	<0.001
≥50% dose, n (%)*	302 (46.6)	234 (32.5)	241 (31.2)	<0.001
MRA, n (%)	347 (42.6)	543 (66.5)	449 (50.7)	<0.001
Digoxin, n (%)	170 (20.9)	192 (23.5)	129 (14.6)	<0.001
All-cause mortality, n (%)	238 (29.2)	197 (24.1)	222 (25.1)	0.043
During up-titration period n(%)	67 (8.2)	43 (5.3)	41 (4.6)	0.004
HF hospitalization	221 (27.1)	171 (21.0)	217 (24.5)	0.014

Legend: ACEi angiotensin converting enzyme inhibitors; ARB angiotensin receptor blocker; BMI body mass index; CABG coronary artery bypass grafting; COPD chronic obstructive pulmonary disease; eGFR estimated glomerular filtration rate; HF heart failure; HR heart rate; JVP jugular venous pressure; LVEF left ventricular ejection fraction; MRA mineralocorticoid receptor antagonist; Nt-proBNP N-terminal pro brain natriuretic peptide; NYHA New York Heart Association; PAD peripheral artery disease; PCI percutaneous coronary intervention; SBP systolic blood pressure.

Table 2 – Baseline characteristics of the BIOSTAT-CHF population by individual country

	Netherlands	France	Germany	Serbia	Slovenia	Greece	Italy	Norway	Sweden	Poland	UK	P Value
Number	407 (16.2)	263 (10.5)	90 (3.6)	385 (15.3)	45 (1.8)	304 (12.1)	319 (12.7)	109 (4.3)	102 (4.1)	296 (11.8)	196 (7.8)	-
Age, y	71.1±11.6	72.4±12.0	66.5±10.1	65.2±9.9	74.6±7.2	66.1±12.2	67.4±12.9	69.5±13.2	71.1±12.7	65.8±11.7	70.2±11.7	<0.001
Male sex, n (%)	257 (63.1)	161 (61.2)	74 (82.2)	307 (79.7)	28 (62.2)	250 (82.2)	263 (82.4)	73 (67.0)	73 (71.6)	215 (72.6)	145 (74.0)	<0.001
Race, n (%)												
White Caucasian	401 (98.5)	262 (99.6)	89 (98.9)	383 (99.5)	45 (100.0)	298 (98.0)	314 (98.4)	106 (97.2)	102 (100.0)	296 (100.0)	193 (98.5)	<0.001
Other	6 (1.5)	1 (0.4)	1 (1.1)	2 (0.5)	-	6 (2.0)	5 (1.6)	3 (2.8)	-	-	3 (1.5)	
BMI, Kg/m ²	27.4±5.3	27.5±6.4	29.6±5.7	27.8±4.7	29.4±5.3	28.2±5.2	27.2±4.6	26.2±5.0	27.4±5.4	28.5±5.3	29.3±7.5	<0.001
HR, bpm	92.1±24.4	81.7±20.2	79.3±23.3	77.1±16.9	76.1±18.3	78.3±17.6	78.2±17.4	88.5±27.3	76.0±17.8	83.3±20.9	86.6±24.9	<0.001
SBP, mmHg	128.2±26.1	122.2±20.3	119.7±17.9	129.2±19.3	131.7±19.4	124.8±21.8	121.0±19.9	124.4±24.3	126.4±22.8	124.0±20.2	118.9±22.2	<0.001
Pulmonary rates, n (%)	252 (63.5)	146 (55.5)	36 (40.9)	141 (36.6)	21 (46.7)	159 (54.3)	188 (59.3)	50 (51.5)	39 (39.4)	166 (56.8)	93 (55.0)	<0.001
Peripheral edema, n (%)	233 (62.6)	146 (55.9)	72 (82.3)	142 (39.4)	22 (51.2)	123 (57.5)	117 (43.2)	41 (64.1)	62 (79.5)	179 (66.1)	119 (66.9)	<0.001
Elevated JVP, n (%)	120 (37.2)	67 (52.8)	13 (17.8)	47 (14.2)	8 (21.6)	60 (37.3)	50 (21.5)	8 (17.8)	35 (44.9)	60 (33.0)	86 (52.4)	<0.001
NYHA class III/IV, n (%)	263 (69.8)	139 (54.1)	71 (78.9)	172 (44.7)	23 (51.1)	186 (61.6)	199 (63.8)	63 (62.4)	72 (72.0)	226 (76.4)	108 (59.7)	<0.001
Orthopnea, n (%)	206 (50.7)	77 (29.4)	36 (40.4)	56 (14.5)	3 (6.7)	132 (43.4)	62 (19.4)	43 (39.8)	20 (19.6)	143 (48.3)	101 (51.8)	<0.001
LVEF, %	32.3±12.9	34.4±11.6	28.9±9.4	28.2±8.5	46.1±16.3	29.1±6.7	29.7±8.8	29.8±10.4	30.2±8.5	32.2±10.7	32.8±12.2	<0.001
Primary HF etiology, n (%)												
Ischemic	161 (39.6)	103 (39.2)	50 (55.6)	186 (48.3)	19 (42.2)	151 (49.7)	151 (47.3)	37 (33.9)	36 (35.3)	126 (42.6)	83 (42.3)	<0.001
Hypertensive	40 (9.8)	36 (13.7)	7 (7.8)	35 (9.1)	19 (42.2)	35 (11.5)	15 (4.7)	9 (8.3)	20 (19.6)	28 (9.5)	10 (5.1)	
Valvular	51 (12.5)	25 (9.5)	7 (7.8)	24 (6.2)	3 (6.7)	16 (5.3)	14 (4.4)	7 (6.4)	4 (3.9)	29 (9.8)	10 (5.1)	
Other/miscellaneous	155 (38.1)	99 (37.6)	26 (28.6)	140 (36.4)	4 (8.9)	102 (33.6)	139 (43.6)	56 (51.4)	42 (41.2)	113 (38.2)	93 (47.4)	
Hemoglobin, g/dL	13.1±2.1	13.0±1.9	13.2±1.8	13.5±1.8	13.1±1.8	13.1±1.8	13.0±1.8	13.1±2.1	13.4±1.6	13.7±1.8	12.7±1.9	<0.001
eGFR, ml/min/1.73m ²	59.4±22.7	56.9±23.0	63.7±22.4	66.0±23.0	55.0±17.5	65.0±22.4	63.9±24.6	65.1±24.1	57.3±21.5	69.1±21.7	55.2±23.0	<0.001
Sodium, mmol/L	139.3±3.8	138.7±3.5	139.0±4.3	140.4±3.3	140.4±3.3	138.1±4.9	139.4±3.7	139.9±3.6	140.2±3.4	139.2±4.1	136.8±4.2	<0.001
Potassium, mmol/L	4.1±0.5	4.1±0.5	4.2±0.5	4.5±0.5	4.8±0.8	4.4±0.6	4.2±0.6	4.3±0.5	4.2±0.4	4.3±0.6	4.3±0.6	<0.001
LogNT-pro BNP, ng/L	3.51±1.36	3.22±1.35	3.14±1.35	2.50±1.37	2.94±1.07	2.74±1.38	2.72±1.29	2.87±1.09	3.33±1.29	3.13±1.40	3.51±1.40	<0.001
Hypertension, n (%)	218 (53.6)	164 (62.4)	80 (88.9)	294 (76.4)	43 (95.6)	179 (58.9)	201 (63.0)	40 (36.7)	53 (52.0)	198 (66.9)	99 (50.5)	<0.001
Atrial Fibrillation, n (%)	191 (46.9)	148 (56.3)	49 (54.4)	129 (33.5)	30 (66.7)	141 (46.4)	126 (39.5)	51 (46.8)	52 (51.0)	133 (44.9)	93 (47.4)	<0.001
Diabetes mellitus, n (%)	113 (27.8)	91 (34.6)	50 (55.6)	110 (28.6)	16 (35.6)	122 (40.1)	110 (34.5)	20 (18.3)	22 (21.6)	104 (35.1)	61 (31.1)	<0.001
COPD, n (%)	94 (23.1)	50 (19.0)	21 (23.3)	49 (12.7)	4 (8.9)	51 (16.8)	66 (20.7)	16 (14.7)	11 (10.8)	40 (13.5)	34 (17.3)	0.001
Stroke, n (%)	45 (11.1)	33 (12.5)	8 (8.9)	24 (6.2)	4 (8.9)	24 (7.9)	25 (7.8)	4 (3.7)	13 (12.7)	31 (10.5)	22 (11.2)	0.063
PAD, n (%)	51 (12.5)	40 (15.2)	22 (24.4)	21 (5.5)	3 (6.7)	32 (10.5)	42 (13.2)	1 (0.9)	8 (7.8)	32 (10.8)	21 (10.7)	<0.001
Device therapy, n (%)	79 (19.7)	69 (26.2)	52 (57.8)	47 (12.2)	2 (4.4)	67 (22.0)	143 (44.8)	16 (14.7)	28 (27.5)	72 (24.3)	43 (21.9)	<0.001
PCI or CABG, n (%)	128 (31.4)	81 (30.8)	58 (64.4)	95 (24.7)	17 (37.8)	127 (41.8)	117 (36.7)	40 (36.7)	27 (26.5)	88 (29.7)	64 (32.7)	<0.001
Loop diuretic, n (%)	406 (99.8)	260 (98.9)	90 (100)	385 (100)	45 (100)	301 (99.0)	317 (99.4)	108 (99.1)	102 (100)	296 (100)	194 (99.0)	0.375
ACEi/ARB, n (%)	270 (66.3)	152 (57.8)	81 (90.0)	321 (83.4)	16 (35.6)	207 (68.1)	224 (70.2)	85 (78.0)	79 (77.5)	222 (75.0)	163 (83.2)	<0.001
≥50% dose, n (%)*	212 (52.1)	130 (49.4)	60 (66.7)	232 (60.3)	29 (64.4)	128 (42.1)	135 (42.3)	67 (61.5)	74 (72.5)	147 (49.7)	98 (50.0)	<0.001
Beta-blocker, n (%)	317 (77.9)	194 (73.8)	88 (97.8)	335 (87.0)	29 (66.4)	246 (80.9)	280 (87.8)	81 (74.3)	87 (85.3)	262 (88.5)	174 (88.8)	<0.001
≥50% dose, n (%)*	215 (52.8)	109 (41.4)	33 (36.7)	112 (29.1)	26 (57.8)	34 (11.2)	121 (37.9)	52 (47.7)	68 (66.7)	94 (31.8)	38 (19.4)	<0.001
MRA, n (%)	157 (38.6)	81 (30.8)	58 (64.4)	284 (73.8)	26 (57.8)	185 (60.9)	183 (57.4)	33 (30.3)	33 (32.4)	175 (59.1)	124 (63.3)	<0.001
Digoxin, n (%)	73 (17.9)	23 (8.7)	20 (22.2)	88 (22.9)	0	44 (14.5)	62 (19.4)	19 (17.4)	11 (10.8)	84 (28.4)	67 (34.2)	<0.001
ACM, n (%)	129 (31.7)	78 (29.7)	27 (30.0)	72 (18.7)	18 (40.0)	78 (25.7)	66 (20.7)	27 (24.8)	26 (25.5)	80 (27.0)	56 (28.6)	<0.001
During up-titration period	42 (10.3%)	19 (7.2)	3 (3.3)	18 (4.7)	5 (11.1)	13 (4.3)	9 (2.8)	8 (7.3)	0	17 (5.7)	17 (8.7)	<0.001
HHF	109 (26.8)	83 (31.6)	22 (24.4)	50 (13.0)	18 (40.0)	56 (18.4)	78 (24.5)	30 (27.5)	31 (30.4)	81 (27.4)	51 (26.0)	<0.001
ACM+HHF	186 (45.7)	124 (47.1)	42 (46.7)	108 (28.1)	27 (60.0)	106 (34.9)	121 (37.9)	47 (43.1)	45 (44.1)	128 (43.2)	83 (42.3)	<0.001

Table 2. Clinical Outcomes by geographic area

	Northern Area	Central Area	Mediterranean Area	Mediterranean vs Northern Area		Mediterranean vs Central Area		Central vs Northern Area	
N. patients	814	816	886	Hazard Ratio (95% CI)		Hazard Ratio (95% CI)		Hazard Ratio (95% CI)	
Outcome	Event rates per 100 person-years			Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
All-cause mortality	16.6	15.0	14.8	0.89 (0.74-1.07)	0.96 (0.77-1.19)	0.99 (0.82-1.20)	0.77 (0.63-0.95)	0.89 (0.74-1.08)	1.23 (0.98-1.55)
HF hospitalization	18.5	17.0	14.7	0.89 (0.74-1.08)	0.91 (0.73-1.14)	1.19 (0.97-1.45)	0.97 (0.79-1.19)	0.75 (0.62-0.92)	0.93 (0.74-1.19)
All-cause mortality +HF hospitalization	30.3	27.6	26.2	0.89 (0.77-1.04)	0.93 (0.77-1.11)	1.07 (0.92-1.25)	0.86 (0.73-1.01)	0.83 (0.71-0.97)	1.07 (0.89-1.29)

*adjusted on age, gender, heart rate, pulmonary congestion, peripheral edema, elevated jugular venous pressure, NYHA class, orthopnea, left ventricular ejection fraction, primary heart failure cause, potassium, Nt-proBNP, hypertension, atrial fibrillation, diabetes, angiotensin converting enzyme inhibitor use and mineralocorticoid receptor antagonist use (i.e. the baseline differences observed from table 1)

Legend: CI confidence interval; HF heart failure.

Figure legend

Figure 1. Individual country contribute to enrollment in the BIOSTAT-CHF study.

Figure 1 Individual country contribute in BIOSTAT-CHF

Figure 2. Treatment according to geographic area

Figure 2. Treatment according to geographic area

Legend: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist. [‡] p=0.026; [*] p=0.001; [†] p=0.001.

Figure 3 (a,b,c). Kaplan-Meier plots according to European region. (a) All-cause mortality and HF hospitalization; (b) all-cause mortality; (c) HF hospitalization

Figure 3c

Figure 4: country-by-country distribution of signs of congestion

Figure 4: country-by-country distribution of signs of congestion

Figure 5: country-by-country distribution of outcomes

Figure 5: country-by-country distribution of outcomes

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