Outcome of Hospitalized Heart Failure in Japan and the United Kingdom Stratified by Plasma N-Terminal Pro-B-Type Natriuretic Peptide

Yasuyuki Shiraishi, MD[1], Toshiyuki Nagai, MD[2], Shun Kohsaka, MD[1], Ayumi Goda, MD[3], Yuji Nagatomo, MD[4], Atsushi Mizuno, MD[5], Takashi Kohno, MD[1], Alan Rigby, MSc[6], Keiichi Fukuda, MD[1], Tsutomu Yoshikawa, MD[4], Andrew L Clark, MD[7] and John GF Cleland, MD[7, 8]

1. Department of Cardiology, Keio University School of Medicine, Tokyo, Japan
2. National Heart & Lung Institute, Imperial College, London, United Kingdom
3. Division of Cardiology, Kyorin University School of Medicine, Tokyo, Japan
4. Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan
5. Department of Cardiology, St, Luke's International Hospital, Tokyo, Japan
6. Academic Cardiology, Castle Hill Hospital, Kingston-upon-Hull, United Kingdom
7. Department of Cardiology, Hull York Medical School, Hull and East Yorkshire Medical Research and Teaching Centre, Castle Hill Hospital, Cottingham, Kingston upon Hull, United Kingdom
8. Robertson Centre for Biostatistics & Clinical Trials, University of Glasgow and National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London, United Kingdom

Corresponding Author:

Shun Kohsaka, MD, PhD

Department of Cardiology

Keio University, School of Medicine

35 Shinanomachi Shinjuku-ku

Tokyo, Japan, 160-8582

TEL: +81-3-3353-1211

FAX: +81-3-5843-6167

E-mail: sk@keio.jp

Total words: 2443 words (including text, figure legends)

ABSTRACT (233 words)

[Background] Mortality subsequent to a hospitalization for heart failure is reported to be much lower in Japan than in the United Kingdom (UK). This could reflect differences in disease severity or in management. Accordingly, we directly compared patient backgrounds and outcomes between Japan and UK.

[Methods] Consecutive patients admitted to academic hospitals in the UK and Japan with heart failure had a common set of variables, including plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP), collected during admission. Mortality during hospitalizations, at 90- and 180-days was recorded and stratified by quintile of NT-proBNP.

[Results] Overall, 935 patients were enrolled; 197 from UK and 738 from Japan. Median (interquartile range) age (UK: 78 [71−88] vs. Japan: 78 [70−84] years; p=0.947), glomerular filtration rate (UK: 49 [34−68] vs. Japan: 49 [33−65] ml/min/1.73m^2; p=0.209) and plasma NT-proBNP (UK: 4957 [2278−10977] vs. Japan: 4155 [1972−9623] ng/L; p=0.186) were similar but systolic blood pressure (SBP) was lower in the UK (118 [105−131] vs. 137 [118−159] mm Hg; p<0.001). Patients with a higher plasma NT-proBNP had a worse prognosis in both countries; in-hospital and post-discharge mortality rates were higher in the UK even after adjusting for prognostic variables including NT-proBNP.

[Conclusions] This analysis suggests that either unobserved differences in patient characteristics or differences in care (formal or informal) rather than greater heart failure severity may account for the worse outcome of heart failure in the UK compared to Japan.

Keywords: Heart failure; N-terminal pro-B-type natriuretic peptide; international comparison; risk stratification; prognosis.

INTRODUCTION

Heart failure is a global problem but patient-outcomes are reported to differ markedly amongst countries,[1,2] despite the similarity of international guidelines on management.[3-10] This may reflect differences in the severity of heart failure, in the implementation of therapy, in patients' willingness to adhere to advice or in ethnicity and culture. Natriuretic peptides provide an objective measure of the severity and prognosis of heart failure and may therefore shed some light on the reasons for observed differences.[11-13] Accordingly, we compared the outcome of patients hospitalized for heart failure in Japan and the United Kingdom (UK) stratified by plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

METHODS

Data sources and study cohort

The characteristics and outcomes of consecutive patients hospitalized for heart failure and who had NT-proBNP measured were recorded in the West Tokyo Heart Failure (WET-HF) registry and the Hull Lifelab registry. Data were collected during 2012 in the UK and between 2011 and 2013 in Japan. WET-HF is an ongoing, prospective, multi-center registry of patients admitted for heart failure to five academic hospitals in metropolitan Tokyo.[14] Data are collected by trained personnel from the patients' charts and entered using a web-based electronic data-capture system. The Hull Lifelab is a large, epidemiologically representative, information-rich data-set on the contemporary diagnosis, treatment and natural history of patients with heart failure with a main focus on out-patient referrals.[15] For this analysis, only patients referred during a hospitalization for heart failure were included.

The clinical diagnosis of heart failure was made by cardiologists with a special interest in heart failure at each institution. The British and Japanese data-sets provide similar information. Each study was approved by the institutional ethics review boards. In Japan, written informed consent is not mandatory and oral informed consent is sufficient based on government rules, for observational studies that use clinical information that has already been obtained as a part of usual clinical practice (the report from the Ministry of Health, labour and Welfare. in only Japanese. www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/). In contrast, written informed consent was obtained from all patients in the UK.

The following data were collected: 1) patient demographics and comorbidities; 2) vital symptoms and signs at presentation; 3) laboratory data including renal function and NT-proBNP measured within 3-5 days after admission; 4) left ventricular ejection fraction (LVEF); 5) medication at discharge; and 6) in-hospital mortality, 90-day and 180-day post-discharge mortality. The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease equation.[16]

Statistical Analysis

We compared patient characteristics, medication at discharge, and mortality between patients in Japan and UK. Categorical variables are expressed as number and percentage, and continuous variables are expressed as the mean ± standard deviation (SD) or the median (interquartile range [IQR]), as appropriate. Statistical comparisons were performed with unpaired t test or Mann-Whitney test for continuous variables and the Pearson's chi-square test for categorical variables. We constructed a prognostic model using logistic regression models rather than Cox proportional hazard models as time-to-event was unknown. Mortality by quintile of plasma NT-proBNP was reported for patients from Japan and the UK; quintile ranges were constructed from the two populations combined. Univariate prognostic model for log-transformed NT-proBNP were constructed for in-hospital, 90-day and 180-day post-discharge mortality. A parsimonious multi-variable prognostic model for 180-day mortality (102 events) were constructed using country of origin and the following nine variables: age, ischaemic heart disease, systolic blood pressure, haemoglobin, serum sodium, eGFR, hsCRP, LVEF, and log-transformed NT-proBNP. Additionally, propensity score matching analysis was performed to evaluate the influence of country on mortality risks after adjusting for the potential imbalance of baseline covariates between countries. Matching was performed using 1:1 matching protocol without replacement, using callipers of width equal to 0.2 of the standard deviation of the propensity score. The balance between the countries in the matching cohort was estimated using the absolute standard difference. All probability values were 2-tailed, and values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed with SPSS version 24.0 software (SPSS Inc., Chicago, Illinois).

RESULTS

Overall, 935 patients were enrolled, including 197 from the UK and 738 from Japan. All patients from the UK and 712 (97.0%) Japanese patients were followed-up for 180 days after discharge. The age and sex distribution of patients enrolled in Japan and the UK were similar (Table 1). However, British patients had a higher body mass index, lower systolic blood pressure (both p<0.001) and more often had ischaemic heart disease, chronic lung disease and a reduced LVEF compared with Japanese patients. However, GFR (UK: 49 [34−68] ml/min/1.73m^2 vs. Japan: 49 [33−65] ml/min/1.73m^2; p=0.209) and plasma NT-proBNP concentrations (UK: 4,957 [2,278−10,977] ng/L vs. Japan: 4,155 [1,972−9,623] ng/L) were similar.

Length of hospital stay (LOHS) was longer in Japan (median [IQR], 13 [9−20] days) compared to the UK (median [IQR], 11 [7−18] days) (p=0.018). Fourteen (7.1%) patients in the UK died during hospitalization compared with 26 (3.5%) in Japan (p=0.027). Mortality rates at 90 days (25 [13.7%] vs. 36 [5.1%]) and 180 days (39 [21.3%] vs. 57 [8.3%]) after discharge were substantially higher among British patients (p<0.001 for each comparison) (Figure 1). In addition, mortality rates were compared by LVEF above and below 45% (Figure 2): there were profound differences in the mortality rates between the Japan and UK cohort, especially among patients with LVEF ≥45%. Several differences were observed in terms of patient characteristics based on LVEF (Table S1; online supplement): among patients with LVEF ≥45%, the British were older and showed a higher level of blood urea nitrogen than that in the Japanese. Medication patterns in patients with LVEF ≥45% also differed between the countries.

In univariate logistic regression models, plasma NT-proBNP was associated with both in-hospital and post-discharge mortality rates in Japan and UK (Table 2). Mortality rose progressively with each higher quintile of NT-proBNP, but within each quintile, mortality was consistently higher amongst British compared to Japanese patients (Figure 3). After multivariate adjustment for country as well as other prognostic indicators, both log-transformed NT-proBNP and country remained independently associated with 180-day post-discharge mortality (Table 3). Even after propensity score matching to further minimize the differences between British and Japanese patients (Table S2; online supplement), country (odds ratio 0.32; 95% confidence interval, 0.13–0.79; p=0.013) was independently

associated with 180-day post-discharge mortality.

DISCUSSION

This analysis suggests that the prognosis of patients hospitalized for heart failure is much better in Japan than in the UK but this does not appear to be due to differences in the severity of heart failure as reflected by plasma concentrations of NT-proBNP. Natriuretic peptides are powerful predictors of both in-hospital and post-discharge mortality, as confirmed for both Japanese and British patients in this study.[11,12] Mortality at 180 days was generally two- to three-times higher within each quintile of NT-proBNP for patients in the UK compared to Japan.

Patients from the UK had several features associated with a worse prognosis including a higher prevalence of ischaemic heart disease and chronic lung disease, lower systolic blood pressure and serum sodium and higher serum urea and hsCRP but also had other features associated with a better prognosis including higher BMI and haemoglobin and slower heart rate. Risk models using similar clinical variables have been shown to be powerful prognostic markers both in Japanese patients and those of European descent.[13,14] However, statistical adjustment in this analysis indicated that observed characteristics only partly accounted for differences in outcome in Japan compared to the UK. There were some treatment differences, including greater use of loop diuretics, ACE inhibitors or angiotensin receptor blockers, MRA and digoxin in the UK and greater use of calcium channel blockers in Japan, perhaps due to a higher prevalence of hypertension as reported in other studies in Japan.[17,18] However, treatment differences did not appear large enough to account for the substantially worse outcome of British patients, especially among patients with preserved ejection fraction, although they might perhaps suggest that patients from the UK had more advanced heart failure.

Our data are derived from just a few hospitals but they do appear to reflect national data in their respective countries. In Japan, LOHS was shorter in this study compared to historical reports,[19] although LOHS may be falling for heart failure in Japan.[20] Despite a longer LOHS in Japan, which increases the risk of in-patient mortality due to the exposure to a greater number of days at risk, in-patient mortality was lower in Japan. An analysis of data from the United States have suggested hat LOHS is associated with an early readmission after discharge,[21] which leads to a higher post-discharge mortality.[22] However, the National Audit for England & Wales suggested that longer LOHS was associated with an

adverse post-discharge prognosis, probably reflecting more severe disease amongst those with longer LOHS.[23] We could not identify such a relationship either for Japanese or British patients in our study. This may reflect the inability to show small differences due to sample size, differences in reasons for LOHS or post-discharge care in Japan and the UK compared to the United States or the absence of any important relationship. LOHS did not result in more patients being discharged on renin-angiotensin-aldosterone system inhibitors or beta-blockers and, historically, patients in Japan are generally treated with lower doses of medication and thus it is difficult to attribute better outcomes in Japan to better treatment due to longer LOHS. The Acute Decompensated Heart Failure Syndromes (ATTEND) registry, which is the largest prospective multi-center registry in Japan, reported an in-hospital mortality of 6.4% and a 180-day mortality of approximately 10%,[18,24] which is similar to the WET-HF registry.

This analysis included data from only one British hospital. However, similar results were reported from the national audit on heart failure for England & Wales including more than 37,000 patients from more than 100 hospitals in 2011−12. The national audit reported a median length of stay on cardiology wards of 9 (IQR 5−16) days, an in-hospital mortality of 11% and a 180-day mortality of approximately 20%.[25] Some reports suggest that mortality rates for patients hospitalized with heart failure might be higher in the UK than other European countries.[26-28] However, the First European Heart Failure survey reported the outcome of >8,000 patients and suggested similar mortality of around 14% within 12 weeks of an admission for heart failure from most of the 24 countries involved.[29] Lower mortalities have been reported in some other European,[26,27] US[28] and Korean[30] registries but this may reflect differences in case-ascertainment which can have a large effect on mortality.

There are many deficiencies in our data that limit interpretation. The cohorts were relatively small but do appear representative of their respective national data. The measurement of NT-proBNP was usually performed several days after hospitalisation rather than on admission. However, this may have been an advantage as BNP measured later during an admission is a stronger marker of prognosis.[31] Differences in variables that were not measured or not included in the statistical model (e.g., frailty, nutritional status, malignancy, or chronic lung disease) may have accounted for the better prognosis of Japanese patients. For example, place of care is a key quality metric for HF. The data from the National Heart Failure Audit for England & Wales showed lower in-hospital as well as post-discharge mortality

rates for patients treated in Cardiology than in General Medicine or other wards.[25] In this British cohort, approximately 40% of patients with HF were admitted to wards other than Cardiology such as General Medicine wards, and this is in agreement with the national data in the UK.[23] However, such data were not obtained pertaining to Japanese patients in this study. Additionally, the national report showed that British patients were more likely to receive specialist follow-up by a cardiologist and/or in a heart failure clinic if treated in a Cardiology ward than in other wards.[23] Therefore, these differences might have affected the outcomes in this study. In addition, evaluation of the mode of death might have helped clarify differences in the prognosis of HF patients between the two countries. Particularly among patients with preserved ejection fraction, further research is warranted to confirm this result by performing a study involving a larger population of patients with HF. A well-designed study that includes comprehensive information regarding biomarkers (e.g., natriuretic peptides, among other such parameters), comorbidities, frailty, social supports and local medical systems may provide a better understanding of the discrepancy between the prognosis of British and Japanese patients with HF. Doses of medication will have been lower in Japan than in the UK but precise data on dose throughout follow-up was not recorded. We have no data on patient-adherence to medical advice or differences in lifestyle choices. Ethnic or genetic differences might also have contributed to differences in outcome and/or response to therapy. Finally, we cannot exclude differences in the criteria for hospitalisation or referral to specialty services or in case-selection. Clearly, these preliminary data require confirmation.

CONCLUSIONS

Important differences exist in patient characteristics, management and outcomes for patients hospitalised with heart failure in Japan compared to the UK but the distribution and prognostic significance of post-admission plasma concentrations of NT-proBNP were similar. Patients in the UK had a substantially higher mortality even after adjusting for plasma NT-proBNP. If the reasons for the difference in mortality can be identified and are modifiable, this might help improve the outcome of patients with heart failure in the UK.

Acknowledgments

We thank Dr. Benjamin Dicken, and other staffs of the WET-HF and Hull Lifelab registries for their

important contributions.

Funding

This research was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KAKENHI No. 21790751) and Butterfield Awards for UK-Japan collaboration in Medicine & Health.

Conflict of interest

Dr. Kohsaka received an unrestricted research grant for the Department of Cardiology, Keio University School of Medicine from Bayer Pharmaceutical Co., Ltd and Daiichi Sankyo Co. Ltd. Dr. Nagai is supported by grants from the Daiichi Sankyo Foundation of Life Science and the Mochida Memorial Foundation for Medical and Pharmaceutical Research. Dr. Cleland acknowledges support from Amgen, Novartis, Medtronic, and Servier. Other authors have no conflicts of interest to disclose. There are no patents, products in development, or marketed products to declare.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The Global Health and Economic Burden of Hospitalizations for Heart Failure: Lessons Learned from HHF Registries. J Am Coll Cardiol 2014;63:1123-1133.
2. Stork S, handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. Epedemiology of heart failure in Germany: a retrospective database study. Clin Res Cardiol 2017;106:913-22.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
5. Howlett JG, Ezekowitz JA, Podder M, Hernandez AF, Diaz R, Dickstein K, Dunlap ME, Corbalan R, Armstrong PW, Starling RC, O'Connor CM, Califf RM, Fonarow GC. Global variation in quality of care among patients hospitalized with acute heart failure in an international trial: findings from the acute study clinical effectiveness of nesiritide in decompensated heart failure trial (ASCEND-HF). Circ Cardiovasc Qual Outcomes 2013;6:534-42.
6. Mentz RJ, Cotter G, Cleland JG, Stevens SR, Chiswell K, Davison BA, Teerlink JR, Metra M, Voors AA, Grinfeld L, Ruda M, Mareev V, Lotan C, Bloomfield DM, Fiuzat M, Givertz MM, Ponikowski P, Massie BM, O'Connor CM. International differences in clinical characteristics,

management, and outcomes in acute heart failure patients: better short-term outcomes in patients enrolled in Eastern Europe and Russia in the PROTECT trial. Eur J Heart Fail 2014;16:614-24.

7. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Bohm M, Lewis EF, Zannad F, Gheorghiade M. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: findings from the ASTRONAUT trial. Eur J Heart Fail 2015;17:591-600.

8. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34-42.

9. Kristensen SL, Martinez F, Jhund PS, Arango JL, Belohlavek J, Boytsov S, Cabrera W, Gomez E, Hagege AA, Huang J, Kiatchoosakun S, Kim KS, Mendoza I, Senni M, Squire IB, Vinereanu D, Wong RC, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJ. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016;37:3167-3174.

10. Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. Circulation 2015;131:43-53.

11. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007;49:1943-50.

12. Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM, Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. Circ Heart Fail 2011;4:628-36.

13. Ouwerkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models

for predicting mortality and/or heart failure hospitalization in patients with heart failure. JACC Heart Fail 2014;2:429-36.

14. Shiraishi Y, Kohsaka S, Abe T, Mizuno A, Goda A, Izumi Y, Yagawa M, Akita K, Sawano M, Inohara T, Takei M, Kohno T, Higuchi S, Yamazoe M, Mahara K, Fukuda K, Yoshikawa T. Validation of the Get With The Guideline-Heart Failure risk score in Japanese patients and the potential improvement of its discrimination ability by the inclusion of B-type natriuretic peptide level. Am Heart J 2016;171:33-9.

15. Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, Wong K, Rigby A, Goode K, Clark AL. Prevalence and Outcomes of Anemia and Hematinic Deficiencies in Patients With Chronic Heart Failure. JAMA Cardiol 2016;1:539-47.

16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.

17. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27:2725-36.

18. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, Murai K, Muanakata R, Yumino D, Meguro T, Kawana M, Nejima J, Satoh T, Mizuno K, Tanaka K, Kasanuki H, Takano T and Investigators A. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. Am Heart J 2010;159:949-955 e1.

19. Kajimoto K, Sato N, Takano T. Relation of left ventricular ejection fraction and clinical features or co-morbidities to outcomes among patients hospitalized for acute heart failure syndromes. Am J Cardiol 2015;115:334-40.

20. Shiraishi Y, Kohsaka S, Harada K, Miyamoto T, Tanimoto S, Iida K, Sakai T, Miyazaki T, Yagawa M, Matsushita K, Furihata S, Sato N, Fukuda K, Yamamoto T, Nagao K, Takayama M. Correlation of Pre- and In-Hospital Systolic Blood Pressure in Acute Heart Failure Patients and the Prognostic Implications- Report From the Tokyo Cardiac Care Unit Network Emergency

Medical Service Database. Circ J 2016;80:2473-2481.

21. Eapen ZJ, Reed SD, Li Y, Kociol RD, Armstrong PW, Starling RC, McMurray JJ, Massie BM, Swedberg K, Ezekowitz JA, Fonarow GC, Teerlink JR, Metra M, Whellan DJ, O'Connor CM, Califf RM, Hernandez AF. Do countries or hospitals with longer hospital stays for acute heart failure have lower readmnission rates?: Findings from ASCEND-HF. Circ Heart Fail 2013;6:727-32.

22. Arundel C, Lam PH, Khosla R, Blackman MR, Fonarow GC, Morgan C, Zeng Q, Fletcher RD, Butler J, Wu WC, Deedwania P, Love TE, White M, Aronow WS, Anker SD, Allman RM, Ahmed A. Association of 30-Day All-Cause readmission with Long-Term Outcomes in Hospitalized Older Medicare Beneficiaries with Heart Failure. Am J Med 2016;129:1178-84.

23. National Heart Failure Audit, April 2015-March 2016. http://www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/annual-report-2015-6-v8.pdf (accessed 8 January 2018)

24. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Muanakata R, Aokage T, Sakata Y, Mizuno K, Takano T. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J 2013;77:944-51.

25. National Heart Failure Audit, April 2011-March 2012. https://www.ucl.ac.uk/nicor/audits/heartfailure/documents/annualreports/hfannual11-12pdf. (accessed 6 May 2017)

26. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Hochadel M, Komajda M, Lopez-Sendon JL, Ponikowski P, Tavazzi L. Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. Eur J Heart Fail 2010;12:239-48.

27. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15:808-17.

28. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG,

Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296:2217-26.

29. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-63.

30. Park JJ, Choi DJ, Yoon CH, Oh IY, Jeon ES, Kim JJ, Cho MC, Chae SC, Ryu KH, Yoo BS, Kang SM, Oh BH. Prognostic value of C-reactive protein as an inflammatory and N-terminal probrain natriuretic peptide as a neurohumoral marker in acute heart failure (from the Korean Heart Failure registry). Am J Cardiol 2014;113:511-7.

31. Cleland JGF, Teerlink JR, Davison BA, Shoaib A, Metra M, Senger S, Milo O, Cotter G, Bourge RC, Parker JD, Jondeau G, Krum H, O'Connor CM, Torre-Amione G, van Veldhuisen DJ, McMurray JJV. Measurement of troponin and natriuretic peptides shortly after admission in patients with heart failure-does it add useful prognostic information? An analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERITAS). Eur J Heart Fail 2017;19:739-747.

Figure Legends

Figure 1. In-hospital, 90-day and 180-day post-discharge mortality rates for patients hospitalized for heart failure in Japan and The United Kingdom.

Figure 2. In-hospital, 90-day and 180-day post-discharge mortality rates based on left ventricular ejection fraction (LVEF): (A) LVEF <45% and (B) LVEF ≥45%.

Figure 3. The mortality rates according to quintiles of plasma concentration of NT-proBNP for the: (2-A) in-hospital mortality; (2-B) 90-day post-discharge mortality; (2-C) 180-day post-discharge mortality. NT-proBNP; N-terminal pro-B-type natriuretic peptide. Quintile ranges were <1641, 1641−3255, 3255−6090, 6090−12340 and >12340 ng/L for the two populations combined.