Socioeconomic status and outcomes in heart failure with reduced ejection fraction from Asia

Short title: Socioeconomic status and outcomes in heart failure

Authors

[*]Tiew-Hwa Katherine Teng,[1,2,3] *MPH, PhD*; [*]Wan Ting Tay,[1] *MAppStat*; Arthur Mark Richards,[4,5] *MD, PhD*; Timothy Shi Ming Chew,[6] *BA*; [†]Inder Anand,[7] *MD, PhD*; Wouter Ouwerkerk,[1,8] *PhD*; Chanchal Chandramouli,[1] *PhD*; Weiting Huang,[1] *MBBS, M Med;* Claire A. Lawson,[9] *PhD*; Umesh T. Kadam,[9] *MBChB, PhD*; Jonathan Yap,[1] *MBBS, M Med*; Shirlynn Lim,[4] *MBBS, M Med*; Chung-Lieh Hung,[10] *MD, PhD*; Michael Ross MacDonald,[11] *MBChB, MD*; Seet Yoong Loh,[12] *MBBS, M Med*; Wataru Shimizu,[13] *MD, PhD*; [#]Jasper Tromp,[1,2,14] *MD, PhD;* [#]Carolyn Su Ping Lam,[1,2,14] *MBBS, PhD*

***** Co-primary authors

Co-senior authors

†On behalf of the ASIAN-HF investigators (Appendix 1)

Affiliations:

1. National Heart Centre Singapore, Singapore
2. Duke-National University of Singapore Medical School, Singapore
3. School of Population & Global Health, University of Western Australia, Australia
4. National University Heart Centre, Singapore
5. University of Otago, New Zealand
6. Claremont McKenna College, California, USA
7. Veterans Affairs Medical Center, University of Minnesota, Minneapolis, U.S.A
8. Amsterdam Medical Center, Department of Dermatology, Amsterdam, The Netherlands

9. University of Leicester, Leicester, U.K.
10. Mackay Memorial Hospital, Taipei, Taiwan
11. Mount Elizabeth Hospital, Singapore
12. Tan Tock Seng Hospital, Singapore
13. Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan
14. University Medical Center Groningen, Department of Cardiology, Groningen, The Netherlands

Word count: 6 560 (All excluding supplementary tables and Appendix 1 – Names of all ASIAN-HF investigators of 46 centers in 11 countries)

****Corresponding Authors:**

Carolyn S.P. Lam, MBBS, PhD

National Heart Centre Singapore

5 Hospital Drive, Singapore 169609

Email: Carolyn.lam@duke-nus.edu.sg

Tel. no: +65 – 6704 2206

Twitter: @lamcardio

Jasper Tromp, MD, PhD

University Medical Center Groningen,

Department of Cardiology, Groningen, The Netherlands

Email: j.tromp01@umcg.nl

Tel. no: +31-6-2386 2386

Abstract

Introduction: Little is known regarding the impact of socioeconomic factors on the use of evidence-based therapies and outcomes in patients with heart failure with reduced ejection fraction (HFrEF) across Asia.

Methods: We investigated the association of both patient-level (household income, education levels) and country-level (regional income level by World Bank classification, income disparity by Gini index) socioeconomic indicators on use of guideline-directed therapy and clinical outcomes (composite of 1-year mortality or HF hospitalization, quality of life [QoL]) in the prospective multinational Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) study.

Results: Among 4,540 patients (mean age: 60±13 years, 23% women) with HFrEF, 39% lived in low-income regions; 34% in regions with high income disparity (Gini ≥42.8%); 64.4% had low monthly household income (<US$1000); and 29.5% had no/ only primary education. The largest disparity in treatment across regional income levels pertained to beta-blocker and device therapies, with patients from low-income regions being less likely to receive these treatments compared to those from high-income regions, and even greater disparity among patients with lower education status and lower household income within each regional income strata. Higher country- and patient- level socioeconomic indicators related to higher QoL scores and lower risk of the primary composite outcome. Notably, we found a significant interaction between regional income level and both household income and education status ($P_{interaction}$ <0.001 for both), where the association of low household income and low education status with poor outcomes was more pronounced in high-income compared to lower income regions.

Conclusion: These findings highlight the importance of socioeconomic determinants among patients with HF in Asia, and suggest that attention should be paid to address disparities in access to care among the poor and less educated, including those from wealthy regions.

Clinical trial registration: ASIAN-HF Registry

ClinicalTrials.gov Identifier: NCT01633398

URL: https://clinicaltrials.gov/ct2/show/NCT01633398

Key words: Socioeconomic status, socioeconomic factors, social class, health status disparities, education, household income, heart failure, low and middle-income countries, high income countries, outcomes, quality of life

Non-standard Abbreviations and Acronyms.

HF	Heart Failure
HFrEF	Heart failure and reduced ejection fraction
QoL	Quality of life
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
LVEF	Left ventricular ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
SD	Standard deviation
NYHA	New York Heart Association
CAD	Coronary artery disease
SES	Socio-economic status
ACEi	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
MRA	Mineralocorticoid receptor antagonists
CKD	Chronic kidney disease
ICD	Implantable cardioverter defibrillator
CRT-D	Cardiac resynchronization therapy-defibrillator
OR	Odds ratio
HR	Hazard ratio

Introduction

Heart Failure (HF) is a critical global public health problem.[1] Many Asian economies are growing rapidly, and large numbers of people are entering into higher socioeconomic status (SES) categories, fueling an epidemiological transition to non-communicable diseases, with downstream increased burden of HF. At the same time, income inequality in much of Asia has worsened[2]. Few Asian countries have universal health insurance coverage and most are more reliant on full or part private payment for healthcare financing, leading to a large inter-country variation in out-of-pocket proportion (7.9%–62.4%) of healthcare expenses.[3] Income disparity and out-of-pocket costs are associated with access to healthcare services and stage of evolution of the national healthcare system, which collectively influence individual health outcomes[4-6]. Several studies have suggested that the wealth of a country and distribution of wealth within a society (income disparity) strongly influence population health.[6-8] Notably, in 2015, the American Heart Association highlighted the most significant opportunities for reducing death and disability from cardiovascular disease lie with addressing the social determinants of outcomes.[9]

Prior studies have shown that regional socioeconomic factors impact outcomes in HF and reduced ejection fraction (HFrEF). Patients with acute HF from lower-income countries in the ASCEND-HF trial had similar mortality rates, but were less likely to be re-hospitalized for HF compared to patients from high income countries, potentially showing differential access to care. [10]. Recent results from the PARADIGM-HF and ATMOSPHERE trials showed that patients from countries with greater income inequality, had worse clinical outcomes.[8] There is, however, a paucity of person-level socio-economic data from low and middle-income countries,[11] particularly from Asia. Moreover, it is unclear whether the observed higher outcomes in the low and middle-income countries are related to use of guideline-directed therapy.

Accordingly, we aimed to investigate the association of both patient-level (household income and education levels) and country-level (regional income level and income disparity) socioeconomic indicators on use of guideline-directed therapy and clinical outcomes (including quality of life [QoL]) in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) study. A better understanding of the impact of SES in HF may provide insights informing refinement of social and health policies to help attenuate the health outcome inequalities pervasive in Asia.

Methods

The study data and materials used to conduct the research cannot be made available to other researchers, for purposes of reproducing the results or replicating the procedure, due to the legal restrictions imposed by multi-national jurisdictions.

The ASIAN-HF registry and study design

The study design and methods of the multinational ASIAN-HF registry had been previously described.[12-14] In brief, the ASIAN-HF registry is a prospective observational registry of Asian patients with HF from 46 medical centres across 11 regions (Taiwan, Hong Kong, China, India, Malaysia, Thailand, Singapore, Indonesia, Philippines, Japan, and Korea). Patients are >18 years of age with symptomatic HF (at least one episode of decompensated HF in the prior 6 months that resulted in hospital admission or treatment in an outpatient clinic). Exclusion criteria included severe valvular heart disease as a primary cause of HF, a life-threatening comorbidity with life expectancy <1 year, or inability or unwillingness to give consent. Patients were enrolled consecutively from the investigation sites (46 in total with >220 investigators) from 1 October 2012 through 31 December 2015. The recruitment sites selected regularly manage and follow patients with chronic HF and include a broad spectrum of medical, cardiology, and HF specialty units. For the purpose of this

study, we included 4540 patients with HFrEF, left ventricular ejection fraction [LVEF] <40%) with data on at least one socio-economic indicator (14% of patients with HFrEF were excluded). Data collected in the registry includes demographic variables, clinical symptoms, functional status, prior cardiovascular investigations, and clinical risk factors. Patients also underwent protocoled 12-lead electrocardiography and transthoracic echocardiography at inclusion.

Socio-economic Indicators

Country-level "macro" socio-economic indicators were: a) national income categorized based on the stage of economic development with the World Health Organization and World Bank classification into '*Low'* – Indonesia, Philippines, and India; '*Middle'* – China, Thailand, and Malaysia and '*High'*– Singapore, Hong Kong, Taiwan, South Korea, and Japan and b) income inequality using the Gini coefficient.[15] Gini coefficients were further divided into tertiles: *1st: Lower (≤35.1%); 2nd: Middle (35.2-42.7%); 3rd: Higher (≥42.8%*). Supplementary Table I shows the classification of regions by national income and Gini coefficients. The Gini coefficient is a measure of the dispersion or distribution of wealth or income representing the income or wealth inequality within a country. The coefficient ranges from 0 (i.e. perfect equality) to 1 (perfect inequality). Gini coefficients are derived from the Lorenz curve framework (income distribution curve), which reflects percentage of income earned by progressive and cumulative proportions of households in the population.[16] Gini coefficients (higher equates to larger income disparity), were obtained from the Central Intelligence Agency-The World FactBook.[17] Data from 2008/2009 were used to account for the lag in effect of income disparity on health; no earlier data was available for many countries in Asia. Where Gini coefficients were not available, values closest to the 2008/2009 were used. Values for Singapore and Hong Kong had to be sourced from The World FactBook.

Patient-level "micro" socio-economic indicators were: monthly household income (in US$) was grouped into three levels as: <1000, 1000-2999, ≥3000; educational status was grouped into four levels as: no formal or primary only, secondary, pre-university and degree or higher education.

Health-related quality of life

Patient-centred health-related QoL was determined using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ is a 23-item, self-administered questionnaire, validated in multiple HF-related disease states and in several languages, assessing the domains of physical function, symptoms, social function, self-efficacy and knowledge, and QoL.[18, 19] An overall summary score can be derived from each domain with scores ranging from 0-100 (higher scores indicating better health status)[18] and a clinically meaningful difference established as five points.[20]

Outcomes

The primary outcome of this study was a composite of all-cause death or HF hospitalization within one year. Patients' QoL and one-year all-cause mortality were the secondary outcomes. For the latter, only death from any cause within one year was considered. Outcome data was available for 4061 (89%) patients, and 11% of patients were lost to follow-up. Patients with less than one year of follow-up were censored at their last known visit date.

Outcomes were adjudicated by an independent event adjudication committee. All data was captured prospectively in an electronic database, with registry operations and data management handled by Quintiles Outcomes as the contract research organization appointed by the academic Executive Committee. Ethics approvals were obtained from the local institutional review committee of each participating centre, which conform to the ethical guidelines as laid down in the Declaration of Helsinki. Informed consent was also received from all participants.

Statistical analysis

Countries were stratified into groups based on country income level and income disparity (Gini coefficient). Standard descriptive statistics were used to describe patients in these groups, as means ± standard deviations (SD), medians (lower quartile, upper quartile) or numbers and proportions. A test of trend across the national income groups and income disparity in tertiles was performed with linear regression and Wilcoxon rank-sum test for continuous and categorical variables respectively. We included patients with data available for education or household income. Patients with missing data were excluded from the analyses by case wise deletion. A sensitivity analysis using missing indicators for missing variables, including the patients with missing responses for the SES variables (monthly household income and education), was also undertaken.

Multivariable Cox regression models, adjusting for age, sex, inpatient enrolment, NYHA class III/IV, BMI, heart rate, systolic blood pressure, history of CAD, atrial fibrillation, peripheral arterial disease, diabetes, chronic kidney disease, smoking, use of ACE-inhibitor or ARB, beta blocker and MRA and national income were used to examine the association of socio-economic indicators and 1-year outcomes. We checked for interaction between patient-level indicators (education levels, monthly household income) and country-level indicators (national income levels, Gini tertiles for income disparity). In presence of significant interactions, further stratified analyses were undertaken. As a sensitivity analysis, to avoid unequal weighting of each region, we undertook bootstrap sampling (with 1000 repetitions) of a random sample of 150 patients from each country/region (PRChina/Hong Kong as one region, Thailand/Philippines as one). Further adjustment was made for patient characteristics, comorbidities, medical and device therapy for the association of SES variables with a composite outcome. We also fitted a mixed effects Weibull regression model, with random intercepts for study sites to account for the variation between sites (and consequently

country/region). The Cox proportional hazards assumption was confirmed using log-log plots and the Schoenfeld residuals test. For all analyses, reported p-values are two-sided, and significant at the 5% level. All analyses were performed using Stata [v14] (College Station, Texas, U.S.A.).

Results

Baseline characteristics

Among 4,540 Asian patients (mean age: 60±13 years, 23% women) with HFrEF, 39% lived in low-income regions (Table 1); 34% in regions with Gini ≥42.8% indicating high income disparity (Supplementary Table II); 64.4% were from the low monthly household income category; and 29.5% had no/ only primary education. A third (34%) of those from high-income regions were also from regions with highest income disparity.

Low-income regions had the highest proportion with low (<$1000) household income (79%, compared to 62.6% in middle-income and 47.5% in high-income regions). In contrast, high-income regions had the highest proportion of patients with no/ only primary education (33.2%, compared to 26.6% in low-income and 29.8% in middle-income regions; $p<0.001$). Compared to patients from high-income regions, those from low-income regions were younger and had a lower overall comorbidity burden except for obesity, which showed a similar prevalence across income regions (Table 1).

Patients residing in regions with high income disparity were more likely to have no/ only primary education (35%) or have low household income (64.4%) compared to patients from regions with low income disparity (25.1% and 37.4% respectively). Comorbidity burden, including obesity, was higher in patients from regions with high income disparity (Supplementary Table II).

At the individual patient level, education level correlated moderately with household income (Pearson's correlation = 0.35). Patients in the lowest educational or lowest household income, relative to higher categories, were more likely to be older, and have concomitant hypertension, diabetes and chronic kidney disease (CKD) (Table 2).

Medication usage

As shown in Figure 1, the largest disparity in treatment across regional income levels pertained to beta-blocker and ICD use. Compared to patients from high-income regions, those from low-income regions were as likely to receive ACEi/ARBs (76.8% vs 77.6%), but less likely to be on beta-blockers (84% vs 64.8%) or have ICDs implanted (4.4% vs 1.9%) (Table 1). For device therapy, use of both ICD/CRT-D and pacemakers were significantly higher in regions of high- (vs. low-) income. The use of pacemakers was strikingly related to education (17.5% high, vs. 6.9% low), and household income [22.2% high (≥$3000/month) vs.5.4% low (<$1000/month), Table 2]. The 25.3% (vs. 8.5%) use of pacemakers in low- (vs. high) income disparity regions was even more remarkable (Supplementary Table II). This was not seen for ICD/CRT-D (Table 1). The associations of patient-level SES variables and regional income with medications and device therapy persisted even after adjustment for patient characteristics and comorbidities (Table 3). When stratified by regional income level, in low-income regions, the underuse of beta-blockers was even more pronounced among patients with no/ only primary education compared to patients with a degree or higher education (odds ratio (OR) 0.57, 95% CI 0.43-0.74; Figure 1A, Table 4). In high-income regions, lower education status and lower household income were also associated with underuse of ACEi/ARBs (OR 0.60, 95% CI 0.42-0.86 and 0.47, 95% CI 0.33-0.67 respectively; all $p \leq 0.005$) and beta-blockers (OR 0.29, 95% CI 0.17-0.48 and 0.39, 95% CI 0.25-0.60 respectively; all $p < 0.001$, Figure 1, Table 4) compared to higher education status and higher household income groups respectively. Low household income or

education were similarly associated with underuse of ACEi/ARBs and beta-blockers in regions with lower income disparity, compared to higher household income and higher education status groups respectively (Supplementary Table III).

Health-related quality of life

Higher regional income level was associated with better overall and individual QoL domains (e.g. physical limitation, symptom burden, total symptom score, social limitation) compared to lower regional income level (Table 1). Patients from high income disparity had significantly poorer functional status and symptoms (with >10 points difference) in clinical summary score despite better self-efficacy score, as compared to those from low-income disparity regions (Supplementary Table II).

Higher educational status and higher household income were associated with better physical limitation, symptom burden and self-efficacy scores, but not social limitation or overall quality of life score, compared to lower educational and household income levels (Table 2). Following multivariable adjustment, higher educational status remained significantly related to better self-efficacy and symptom scores (6-10 points improvement in adjusted mean scores) (p for trend across education categories <0.001) compared to those with no/ only primary education.

Clinical Outcomes

In total, 754 (19%) of the cohort had a composite event (all-cause mortality or hospitalization for HF within 1 year). The 1-year composite event rate was 13.8%, 21.1% and 21.7% in low-, middle- and high-income regions (p<0.001) (Table 1); and 15.6%, 13.8% and 26.2% in lower, middle and higher disparity regions (p<0.001) (Supplementary Table II) respectively. A low household income or no/ only primary education was associated with higher rates of the primary composite outcome compared

to higher household income and higher educational levels respectively (Table 2). On multivariable adjustment for patient characteristics, comorbidities and processes of care (ACEi/ARBs, β-blockers and all device therapies), low education and high regional income remained significantly associated with the composite outcome, whereas household income was not. Use of ACEi/ARB and beta-blockers was also found to be associated with lower hazards of 1-year composite outcome. The addition of the variables for processes of care did not affect the associations of the SES variables in relation to the outcomes (Table 5). Notably, we found a significant interaction between regional income level and both household income and education status ($P_{interaction}$ <0.001 for both), where the association of low household income and low education status with poor outcomes was more pronounced in high-income compared to lower income regions (Figure 2A, Table 6). On the other hand, only low education status ($P_{interaction}$ = 0.024) was associated with poor outcomes in patients from regions with lower income disparity compared to higher income disparity (Supplementary Table IV).

Mortality was not independent of admission (p<0.001); 19% of patients who had a hospitalization within the year eventually died whereas 10% of patients died within the year without any prior hospitalizations.

As a sensitivity analysis, patient-level SES indicator of low education (vs high education) was still associated with higher hazards of the composite outcome, after taking into account equal weightage of each region/country in the bootstrapped sample and adjustment for patient characteristics, medical and device therapy. Low household income (vs high household income) showed the trend towards higher hazards of the composite outcome (Supplementary Table V). With the Weibull mixed effects model to account for variation across the 46 sites, patient-level SES indicator of low education (vs high education) was associated with higher hazards of the composite outcome in the univariable

model. The association was however attenuated after extensive adjustment for patient characteristics, comorbidities, medical and device therapy. Supplementary Table VI showed the decomposed events for the three (*Low, Middle, High)* income regions.

Discussion

Social determinants of health present significant opportunities for reducing death and health disparities. In our large prospective multinational cohort of patients with HFrEF across 11 regions in Asia, we found that both patient-level (household income and education levels) and country-level (regional income level and income disparity) socioeconomic indicators were associated with the use of guideline-directed therapy, QoL and clinical outcomes. Patients from low-income regions, with lower educational status and lower household income were least likely to receive guideline-directed therapies and had the lowest QoL scores. Yet, it was the "rich-poor" i.e. those from high-income regions, but with low household income and less education, who had the worst clinical outcomes (death and HF hospitalization in 1 year). These findings highlight the importance of socioeconomic determinants in HF and suggest that attention should be paid to address disparities in access to care among the poor and less educated, including the vulnerable "rich poor". Further, the findings showed a strong role for social factors, even after adjusting for medical/device therapy, in influencing health outcomes in HF across settings. The inter-play of the wider set of social factors and systems at both patient level and importantly the macro environment (country level) on clinical outcomes warrant further investigation.

Asia has achieved remarkable economic growth in recent decades. Nevertheless, poverty remains a key issue to be addressed as half of the world's poorest people are housed in Asia.[21] Rapid urbanization risks widening inequalities of the poor and marginalized; not surprisingly, the poor and less educated have the worst outcomes. Our current data showed that patients with low education

status and low household income were particularly susceptible to worse access to care, evident from the lower use of evidence-based medical therapy. This is consistent with our prior study focused on device therapy (ICDs/CRT-Ds) in HFrEF [22] where we observed that education status had the strongest positive association with the uptake of ICDs, with "tertiary" (vs. "primary and lower") educated patients being 5.5 times more likely to have an ICD implanted; in contrast, patients' household income was not found to be associated with ICD implantation. At a macro level, the higher national economic status was also related to higher ICD utilization, reflecting in part, the cost burden of ICD devices. However, low health literacy about the benefits of device therapy was a barrier to patients' acceptance of ICD implantation, underscoring the need for better patient education. It is noteworthy that in our current study higher educational status was independently related to better self-efficacy and symptom scores among patients. Thus both patient-level and country-level socioeconomic factors may contribute to health outcomes, while factors such as individual ability to navigate the health care system, educational disparities in personal health behaviors, and exposure to chronic stress may act as more proximate factors.

Two previous studies investigated the association between country level income or country level income disparity and outcomes in HF. Both studies found that clinical outcomes were generally worse in patients from higher income countries[10] and countries with greater income disparity.[8] In the higher income countries, the poorer outcomes were largely driven by higher rates of rehospitalization,[10] potentially reflecting differential access to care compared to those in low-middle-income countries. Our paper extends upon these previous findings by showing that there is important within region heterogeneity, where particularly patients with low education status and low household income in high income countries have the worst clinical outcomes and lower uptake of evidence-based medications, reflecting a greater relative under-privilege of the poor in wealthy countries. Our

data might also reflect a steeper 'wealth gradient' in high-income regions, in contrast to the flatter 'wealth gradient' in poor regions, which further highlights the important context of 'place', i.e. not just 'being poor but where' that matters most. Apart from the lower use of evidence-based therapy, a potential explanation is the chronic stress as a consequence of income disparity which increases status competition, particularly being in economically advanced countries, leading to adverse psychoneuroendocrine effects, poor health and poor self-esteem.[8, 23]. In our study, we used monthly household income and patient-level education status as elements for SES. Our finding that lower SES associates with higher all-cause mortality and HF hospitalizations is consistent with published studies.[11, 24-28]. Few studies have used patient-level data in examining the association of SES with QoL and clinical outcomes. An equivocal association with outcomes has been reported, possibly due to use of area-based indicators instead of patient-level data.[25, 29]

"Unpacking" the reasons for the connection between education and health outcomes is essential to setting policy priorities. Additionally, further understanding of the intersections of health and social exposures over the life-course at different levels (individual and environmental) settings need to be carefully untangled.

The strengths of our study lie in using patient-level data unlike many studies which made use of area-based indicators. We examined SES as a multi-dimensional construct using macro and micro SES indicators and their association with QoL and hard outcomes, across a vast geography in Asia encompassing different stages of economic development. The analysis was comprehensively adjusted for clinical factors, comorbidities, pharmacological treatment and device therapy. We acknowledged potential within-country variation of income level, healthcare delivery and other factors that cannot be fully accounted for. Furthermore, differences in purchasing power parity across regions was

however unaccounted for in the absence of truly contemporary indicators, and we could not account for residual confounding by unknown and unmeasured factors in our analyses.

Conclusions

These first prospective multinational data on both patient-level (household income and education levels) and country-level (regional income level and income disparity) socioeconomic indicators among patients with HFrEF across Asia highlight the important associations of socioeconomic determinants with access to evidence-based therapies, QoL and clinical outcomes. The largest disparity in treatment across regional income levels pertained to beta-blocker and device therapies, with patients from low-income regions being less likely to receive these treatments compared to those from high-income regions, and even greater disparity among patients with lower education status and lower household income within each regional income strata. Higher country- and patient- level socioeconomic indicators related to higher QoL scores and lower risk of the primary composite outcome. Our results further highlighted the "rich poor" as an especially vulnerable group – these were patients from high-income regions with low household income and low education status, who had the worst outcomes of all. Attention should be paid to address disparities in access to care among the poor and less educated, including those from wealthy regions.

Acknowledgements

The contribution of all site investigators and clinical coordinators are duly acknowledged.

Funding

The ASIAN-HF is supported by research grants from Boston Scientific Investigator Sponsored Research Program, National Medical Research Council of Singapore (R-172-003-219-511), A*STAR Biomedical Research Council Asian neTwork for Translational Research and

Cardiovascular Trials (ATTRaCT) program (SPF2014/003, SPF2014/004, SPF2014/005), and Bayer.

Authors' contributions

CSPL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors critically reviewed and contributed to the intellectual content of the manuscript.

Declaration of interests

None relevant to the present work.

C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder & non-executive director of eKo.ai.

AMR has received research support from Boston Scientific, Bayer, Astra Zeneca, Medtronic, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics and has consulted for Bayer, Novartis, Merck, Astra Zeneca, Roche Diagnostics.

List of supplementary materials

Supplementary Table I: Country classification based on regional income level and Gini coefficient (a measure of income disparity), as macro SES indicators

Supplementary Table II: Baseline characteristics according to Gini coefficient [as tertiles -1st Lower income (Y) disparity, 2nd Middle Y disparity, 3rd High Y disparity]

Supplementary Table III: Associations of lower education status and lower household income with use of ACEi/ARBs and beta-blockers, stratified by income disparity

Supplementary Table IV: Association of education and household income with 1-year composite outcome, stratified by income disparity

Supplementary Table V: Association of education and household income with 1-year composite outcome (sensitivity analyses using (1) bootstrap sampling and (2) missing indicators for missing variables)

Supplementary Table VI: The decomposed events for the three (*Low, Middle, High*) income regions

References

1. Savarese G and Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3:7-11.

2. Kanbur R, Rhee C and Zhuang J. Inequality in Asia and the Pacific: Trends, drivers, and policy implications. 2014. https://www.adb.org/sites/default/files/publication/41630/inequality-asia-and-pacific.pdf (accessed on 18 October 2018).

3. Chia YMF, Teng TK, Tan ESJ, Tay WT, Richards AM, Chin CWL, Shimizu W, Park SW, Hung CL, Ling LH et al. Disparity Between Indications for and Utilization of Implantable Cardioverter Defibrillators in Asian Patients With Heart Failure. *Circ Cardiovasc Qual Outcomes*. 2017;10:1-10.

4. Sumarsono A, Vaduganathan M, Ajufo E, Navar AM, Fonarow GC, Das SR and Pandey A. Contemporary Patterns of Medicare and Medicaid Utilization and Associated Spending on Sacubitril/Valsartan and Ivabradine in Heart Failure. *JAMA Cardiol*. 2020;5:336-339.

5. Murphy A, Palafox B, O'Donnell O, Stuckler D, Perel P, AlHabib KF, Avezum A, Bai X, Chifamba J, Chow CK et al. Inequalities in the use of secondary prevention of cardiovascular disease by socioeconomic status: evidence from the PURE observational study. *Lancet Glob Health*. 2018;6:e292-e301.

6. Khatib R, McKee M, Shannon H, Chow C, Rangarajan S, Teo K, Wei L, Mony P, Mohan V, Gupta R et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet*. 2016;387:61-9.

7. Pickett KE and Wilkinson RG. Income inequality and health: a causal review. *Soc Sci Med*. 2015;128:316-26.

8. Dewan P, Rorth R, Jhund PS, Ferreira JP, Zannad F, Shen L, Kober L, Abraham WT, Desai AS, Dickstein K et al. Income Inequality and Outcomes in Heart Failure: A Global Between-Country Analysis. *JACC Heart Fail*. 2019;7:336-346.

9. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, Davey-Smith G, Dennison-Himmelfarb CR, Lauer MS, Lockwood DW et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2015;132:873-98.

10. Greene SJ, Hernandez AF, Sun JL, Butler J, Armstrong PW, Ezekowitz JA, Zannad F, Ferreira JP, Coles A, Metra M et al. Relationship Between Enrolling Country Income Level and Patient Profile, Protocol Completion, and Trial End Points. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004783.

11. de Mestral C and Stringhini S. Socioeconomic Status and Cardiovascular Disease: an Update. *Curr Cardiol Rep*. 2017;19:115.

12. Lam CS, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB et al. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail*. 2013;15:928-36.

13. Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T et al. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. *Eur Heart J*. 2016;37:3141-3153.

14. Tromp J, Teng TH, Tay WT, Hung CL, Narasimhan C, Shimizu W, Park SW, Liew HB, Ngarmukos T, Reyes EB et al. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail*. 2019;21:23-36.

15. Farris F. The Gini Index and Measures of Inequality *The American Mathematical Monthly*. 2010;117:336-339.

16. Gini coefficient. Available at: https://en.wikipedia.org/wiki/Gini_coefficient. Accessed on 6 September 2020

17. The Central Intelligence Agency - The World FactBook. United Nations. United Nations Development Programme. Income Gini Coefficient. Human Development Reports. 2013. Available at: http://hdr.undp.org/en/content/income-gini-coefficient . Accessed 12 June 2019.

18. Green CP, Porter CB, Bresnahan DR and Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35:1245-55.

19. Luo N, Teng TK, Tay WT, Anand IS, Kraus WE, Liew HB, Ling LH, O'Connor CM, Pina IL, Richards AM et al. Multinational and multiethnic variations in health-related quality of life in patients with chronic heart failure. *Am Heart J*. 2017;191:75-81.

20. Butler J, Khan MS, Mori C, Filippatos GS, Ponikowski P, Comin-Colet J, Roubert B, Spertus JA and Anker SD. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2020;22:999-1005.

21. World Bank. Poverty Overview 2018. Available from: https://www.worldbank.org/en/topic/poverty/overview (accessed on 20 August 2019).

22. Chia YMF, Teng TK, Tan ESJ, Tay WT, Richards AM, Chin CWL, Shimizu W, Park SW, Hung CL, Ling LH et al. Disparity Between Indications for and Utilization of Implantable Cardioverter Defibrillators in Asian Patients With Heart Failure. *Circ Cardiovasc Qual Outcomes*. 2017;10.

23. Kim D, Kawachi I, Hoorn SV and Ezzati M. Is inequality at the heart of it? Cross-country associations of income inequality with cardiovascular diseases and risk factors. *Soc Sci Med*. 2008;66:1719-32.

24. Khariton Y, Nassif ME, Thomas L, Fonarow GC, Mi X, DeVore AD, Duffy C, Sharma PP, Albert NM, Patterson JH et al. Health Status Disparities by Sex, Race/Ethnicity, and Socioeconomic Status in Outpatients With Heart Failure. *JACC Heart Fail*. 2018;6:465-473.

25. Verma AK, Schulte PJ, Bittner V, Keteyian SJ, Fleg JL, Pina IL, Swank AM, Fitz-Gerald M, Ellis SJ, Kraus WE et al. Socioeconomic and partner status in chronic heart failure: Relationship to exercise capacity, quality of life, and clinical outcomes. *Am Heart J*. 2017;183:54-61.

26. Hawkins NM, Jhund PS, McMurray JJ and Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. *Eur J Heart Fail*. 2012;14:138-46.

27. Woodward M, Peters SA, Batty GD, Ueshima H, Woo J, Giles GG, Barzi F, Ho SC, Huxley RR, Arima H et al. Socioeconomic status in relation to cardiovascular disease and cause-specific mortality: a comparison of Asian and Australasian populations in a pooled analysis. *BMJ open*. 2015;5:e006408.

28. Rathore SS, Masoudi FA, Wang Y, Curtis JP, Foody JM, Havranek EP and Krumholz HM. Socioeconomic status, treatment, and outcomes among elderly patients hospitalized with heart failure: findings from the National Heart Failure Project. *Am Heart J*. 2006;152:371-8.

29. Stringhini S, Carmeli C, Jokela M, Avendano M, Muennig P, Guida F, Ricceri F, d'Errico A, Barros H, Bochud M et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. *Lancet*. 2017;389:1229-1237.

Figure Legends

Figure 1: Usage of medications and ICD by (A) regional income and education status; (B) regional income and household income status

ACEi/ARB: Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BBL: beta-blockers; MRA: mineralocorticoid receptor antagonists; ICD: implantable cardioverter defibrillator

Figure 2: (A) 1-year composite outcome and (B) 1-year mortality, by regional income and education status or household income status

Table 1: Baseline characteristics according to regional income (as a macro socioeconomic status (SES) indicator) based on World Bank classification

Baseline characteristics	% missing	Regional income (Y) Low Y	Middle Y	High Y	p trend
N		**1776**	**1167**	**1597**	
Socio-demographic indicators					
Education, n (%)	0.7%				<0.001
No/only primary		471 (26.6%)	344 (29.8%)	525 (33.2%)	
Secondary		599 (33.8%)	509 (44.0%)	555 (35.1%)	
Pre-University/ITE		213 (12.0%)	184 (15.9%)	231 (14.6%)	
Degree/higher		491 (27.7%)	119 (10.3%)	269 (17.0%)	
Monthly household income (USD), n (%)	12.8%				<0.001
<1000		1249 (79.0%)	612 (62.6%)	666 (47.5%)	
1000-2999		237 (15.0%)	265 (27.1%)	433 (30.9%)	
>=3000		95 (6.0%)	101 (10.3%)	303 (21.6%)	
Age (years), [mean (SD)]	0.1%	57.7 (12.4)	58.0 (13.1)	64.0 (13.2)	<0.001
Women, n (%)	0.0%	415 (23.4%)	230 (19.7%)	389 (24.4%)	0.544
Geographical region, n (%)	0.0%				<0.001
Northeast Asia		0 (0.0%)	461 (39.5%)	1114 (69.8%)	
South Asia		1397 (78.7%)	0 (0.0%)	0 (0.0%)	
Southeast Asia		379 (21.3%)	706 (60.5%)	483 (30.2%)	
Clinical examination					
Enrolment as in-patient, n (%)	0.0%	624 (35.1%)	571 (48.9%)	622 (38.9%)	0.014
NYHA class III/IV, n (%)	9.4%	648 (41.1%)	442 (39.9%)	425 (29.7%)	<0.001
LV ejection fraction (%), [mean (SD)]	0.0%	28.0 (6.2)	27.5 (7.3)	27.3 (7.7)	0.011
Heart rate, bpm [mean (SD)]	0.7%	82.3 (16.4)	77.7 (15.8)	78.5 (16.1)	<0.001
Systolic blood pressure (mmHg), [mean (SD)]	0.6%	116.4 (19.3)	119.1 (19.4)	120.0 (21.1)	<0.001
Diastolic blood pressure (mmHg), [mean (SD)]	0.6%	74.3 (11.5)	72.7 (12.3)	71.0 (13.7)	<0.001
Estimated GFR (mL/min/1.73m^2), [mean (SD)]	23.8%	69.3 (30.9)	66.4 (26.0)	63.9 (27.2)	<0.001
Medical history, n (%)					
Ischemic aetiology of heart failure	0.2%	768 (43.3%)	554 (47.8%)	722 (45.2%)	0.964
Coronary artery disease	0.3%	931 (52.6%)	565 (48.7%)	729 (45.6%)	<0.001
Atrial fibrillation/flutter	0.2%	97 (5.5%)	225 (19.4%)	475 (29.7%)	<0.001
Hypertension	0.2%	720 (40.6%)	635 (54.7%)	915 (57.3%)	<0.001
Diabetes	0.2%	691 (39.0%)	449 (38.7%)	718 (45.0%)	0.001
Prior stroke	0.3%	53 (3.0%)	60 (5.2%)	145 (9.1%)	<0.001
Peripheral arterial vascular disease	0.3%	29 (1.6%)	37 (3.2%)	67 (4.2%)	<0.001
Chronic respiratory disease	0.3%	104 (5.9%)	105 (9.1%)	162 (10.1%)	<0.001
CKD (eGFR <60mL/min/1.73m^2)	23.8%	484 (40.6%)	336 (41.4%)	677 (46.5%)	0.002
Obesity (BMI ≥27.5 kg/m^2)	4.9%	385 (23.1%)	265 (24.2%)	349 (22.5%)	0.716

Lifestyle factors, n (%)					
Smoking history (Yes)	0.3%	515 (29.1%)	604 (52.1%)	832 (52.1%)	<0.001
Alcohol intake (Yes)	0.3%	318 (18.0%)	379 (32.7%)	553 (34.6%)	<0.001
Medications/devices, n (%)					
ACEi or ARB	2.2%	1336 (77.6%)	741 (65.4%)	1217 (76.8%)	0.472
Beta blockers	2.2%	1115 (64.8%)	917 (80.9%)	1331 (84.0%)	<0.001
MRA	2.2%	982 (57.1%)	775 (68.4%)	842 (53.1%)	0.033
Loop diuretics	2.2%	1399 (81.3%)	919 (81.1%)	1239 (78.2%)	0.026
Device use	0.2%				<0.001
ICD/CRT-D		34 (1.9%)	49 (4.2%)	70 (4.4%)	
Pacemakers		78 (4.4%)	114 (9.8%)	308 (19.3%)	
Quality of life, mean (SD)					
KCCQ Physical Limitation Score	4.6%	64.6 (25.1)	65.7 (25.9)	73.0 (25.6)	<0.001
KCCQ Symptom Stability Score	4.1%	61.0 (27.2)	67.0 (26.9)	62.5 (27.9)	0.095
KCCQ Symptom Frequency Score	3.9%	66.5 (26.1)	68.1 (27.2)	70.9 (27.9)	<0.001
KCCQ Symptom Burden Score	3.6%	70.0 (25.0)	69.5 (26.3)	74.5 (26.3)	<0.001
KCCQ Total Symptom Score	3.6%	68.2 (24.7)	68.8 (25.8)	72.7 (26.1)	<0.001
KCCQ Self-Efficacy Score	3.7%	66.0 (28.8)	66.5 (26.2)	61.6 (25.9)	<0.001
KCCQ Quality of Life Score	3.5%	58.6 (25.9)	50.4 (25.0)	58.7 (24.4)	0.993
KCCQ Social Limitation Score	10.5%	61.3 (32.2)	58.1 (31.6)	65.0 (32.4)	0.003
KCCQ Overall Summary Score	3.1%	63.2 (22.7)	60.9 (23.6)	67.5 (22.4)	<0.001
KCCQ Clinical Summary Score	3.1%	66.4 (22.5)	67.3 (23.6)	72.9 (22.8)	<0.001
1-year composite outcome, n (%)	10.6%	211 (13.8%)	220 (21.1%)	323 (21.7%)	<0.001

Explanatory notes: NYHA – New York Heart Association; GFR – glomerular filtration rate; CKD – chronic kidney disease; BMI – body mass index; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; MRA – mineralocorticoid receptor antagonist; ICD – implantable cardioverter defibrillator; CRT-D – cardiac resynchronization therapy-defibrillator; KCCQ – Kansas City Cardiomyopathy Questionnaire

1 **Table 2: Baseline characteristics according to patients' socioeconomic status (SES) measures: education level and monthly household income**

	Highest education level					Monthly household income (USD)			
Characteristic	**No/ only primary**	**Secondary**	**Pre-Uni**	**Degree or higher**	**p trend**	**<1000**	**1000-2999**	**≥3000**	**p trend**
N	**1340**	**1663**	**628**	**879**		**2527**	**935**	**499**	
Age (years), [mean (SD)]	64.2 (12.0)	58.7 (12.4)	57.2 (14.3)	58.2 (13.9)	<0.001	60.7 (13.2)	59.2 (12.9)	58.6 (13.1)	<0.001
Women, n (%)	467 (34.9%)	333 (20.0%)	110 (17.5%)	116 (13.2%)	<0.001	638 (25.2%)	166 (17.8%)	89 (17.8%)	<0.001
Clinical examination									
Inpatient enrolment, n (%)	475 (35.4%)	690 (41.5%)	305 (48.6%)	337 (38.3%)	0.017	966 (38.2%)	371 (39.7%)	199 (39.9%)	0.371
NYHA Class III/IV, n (%)	456 (36.6%)	579 (38.1%)	209 (37.5%)	255 (33.4%)	0.174	882 (38.4%)	271 (32.8%)	136 (29.6%)	<0.001
LVEF (%), [mean (SD)]	27.7 (6.9)	27.4 (7.1)	27.8 (7.2)	27.8 (6.9)	0.603	27.5 (6.8)	27.3 (7.5)	27.5 (7.1)	0.795
Heart rate (bpm), [mean (SD)]	79.7 (15.5)	80.3 (16.5)	79.7 (16.8)	79.3 (16.8)	0.514	80.6 (16.4)	79.9 (16.4)	76.9 (15.5)	<0.001
Systolic BP (mmHg), [mean (SD)]	120.0 (20.3)	118.5 (20.5)	116.8 (19.2)	116.6 (19.4)	<0.001	118.4 (19.4)	120.1 (21.9)	115.4 (19.1)	0.107
Diastolic BP (mmHg), [mean (SD)]	72.2 (11.7)	73.5 (13.1)	71.9 (13.2)	72.6 (12.3)	0.948	72.6 (12.0)	74.1 (13.7)	71.3 (13.3)	0.550
Medical history, n (%)									
Coronary artery disease	649 (48.6%)	824 (49.6%)	295 (47.1%)	435 (49.8%)	0.833	1306 (51.8%)	439 (47.1%)	207 (41.5%)	<0.001
Atrial fibrillation	254 (19.0%)	282 (17.0%)	107 (17.1%)	148 (16.9%)	0.223	370 (14.7%)	184 (19.7%)	116 (23.2%)	<0.001
Hypertension	729 (54.6%)	823 (49.5%)	285 (45.5%)	416 (47.6%)	<0.001	1253 (49.7%)	484 (51.9%)	233 (46.7%)	0.581
Diabetes	552 (41.3%)	698 (42.0%)	248 (39.6%)	348 (39.8%)	0.340	1077 (42.7%)	383 (41.1%)	174 (34.9%)	0.002
Prior stroke	80 (6.0%)	90 (5.4%)	36 (5.8%)	50 (5.7%)	0.854	150 (6.0%)	49 (5.3%)	26 (5.2%)	0.387
Peripheral arterial vascular disease	48 (3.6%)	45 (2.7%)	19 (3.0%)	20 (2.3%)	0.110	74 (2.9%)	29 (3.1%)	13 (2.6%)	0.823
COPD	128 (9.6%)	124 (7.5%)	43 (6.9%)	75 (8.6%)	0.304	197 (7.8%)	86 (9.2%)	44 (8.8%)	0.247
CKD (eGFR <60mL/min/1.73m2)	494 (51.0%)	520 (41.6%)	191 (38.7%)	281 (39.1%)	<0.001	857 (47.5%)	320 (42.5%)	144 (34.1%)	<0.001
Obesity (BMI ≥27.5 kg/m^2)	293 (22.5%)	366 (23.1%)	148 (25.1%)	182 (22.4%)	0.768	531 (22.1%)	232 (26.7%)	109 (22.6%)	0.182
Lifestyle factors, n (%)									
Smoking history (Yes)	536 (40.1%)	797 (47.9%)	268 (42.8%)	333 (38.1%)	0.173	1014 (40.3%)	447 (48.0%)	250 (50.1%)	<0.001
Alcohol intake (Yes)	318 (23.8%)	485 (29.2%)	181 (28.9%)	259 (29.6%)	0.004	570 (22.6%)	295 (31.7%)	204 (40.9%)	<0.001
Medications/devices, n (%)									

ACEi/ARBs	974 (73.8%)	1228 (75.6%)	434 (70.5%)	640 (75.3%)	0.980	1824 (73.7%)	680 (74.2%)	392 (80.2%)	0.009
β - blockers	942 (71.4%)	1253 (77.2%)	486 (78.9%)	656 (77.2%)	0.001	1786 (72.1%)	716 (78.1%)	414 (84.7%)	<0.001
MRAs	758 (57.5%)	985 (60.7%)	375 (60.9%)	465 (54.7%)	0.292	1456 (58.8%)	524 (57.1%)	277 (56.6%)	0.275
Device therapy					<0.001				<0.001
ICD/CRT-D	49 (3.7%)	56 (3.4%)	24 (3.8%)	23 (2.6%)		77 (3.1%)	31 (3.3%)	16 (3.2%)	
Pacemakers	92 (6.9%)	177 (10.6%)	76 (12.1%)	153 (17.5%)		137 (5.4%)	135 (14.5%)	111 (22.2%)	
Quality of life, mean (SD)									
Physical Limitation Score	66.7 (26.0)	67.5 (25.8)	67.7 (25.5)	71.1 (25.3)	<0.001	67.3 (25.9)	70.1 (25.4)	71.7 (25.3)	<0.001
Symptom Stability Score	62.2 (27.5)	64.2 (27.6)	63.2 (28.9)	62.5 (26.1)	0.889	63.3 (27.5)	60.8 (27.6)	62.7 (25.9)	0.184
Symptom Frequency Score	67.4 (26.8)	67.2 (27.8)	68.6 (26.9)	72.5 (26.4)	<0.001	66.9 (27.1)	71.2 (27.5)	72.1 (27.2)	<0.001
Symptom Burden Score	70.5 (26.1)	70.8 (25.8)	70.7 (25.8)	75.2 (25.7)	<0.001	70.7 (25.8)	73.3 (26.0)	75.0 (25.7)	<0.001
Total Symptom Score	68.9 (25.4)	69.0 (25.9)	69.7 (25.4)	73.8 (25.2)	<0.001	68.8 (25.5)	72.2 (25.9)	73.6 (25.4)	<0.001
Self-Efficacy Score	56.5 (28.3)	65.5 (26.5)	70.4 (27.3)	71.8 (23.3)	<0.001	62.8 (28.1)	64.3 (25.7)	67.3 (24.3)	0.001
Quality of Life Score	57.4 (25.0)	55.7 (25.1)	54.9 (26.8)	57.7 (25.5)	0.940	57.4 (25.6)	55.4 (24.9)	57.6 (25.2)	0.497
Social Limitation Score	63.3 (32.7)	61.3 (32.0)	59.7 (31.3)	61.5 (32.7)	0.133	63.1 (32.2)	62.3 (31.6)	61.2 (32.5)	0.228
Overall Summary Score	64.2 (23.1)	63.5 (23.0)	63.1 (23.0)	66.2 (22.8)	0.098	64.2 (23.0)	65.3 (22.8)	66.2 (23.0)	0.053
Clinical Summary Score	67.9 (22.8)	68.2 (23.3)	68.7 (23.0)	72.5 (22.8)	<0.001	68.1 (23.1)	71.3 (22.9)	72.8 (22.9)	<0.001
1-year composite outcome, n (%)	267 (22.5%)	286 (19.4%)	89 (15.2%)	106 (13.4%)	<0.001	451 (20.2%)	123 (14.4%)	70 (15.3%)	<0.001

1 Explanatory notes: NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; COPD – chronic obstructive pulmonary disease;
2 CKD – chronic kidney disease; BMI – body mass index; ACEi/ARB – angiotensin-converting enzyme inhibitors/angiotensin receptor blockers;
3 MRAs – mineralocorticoid receptor antagonists; ICD/CRT-D – implantable cardioverter defibrillator/cardiac resynchronization therapy -
4 defibrillator

Table 3: Association of education status, monthly household income and regional income with medications and device therapy, adjusted for patients' characteristics and comorbidities

	ACEi/ARB		Beta-blocker		Device therapy	
	Odds ratio* (95% CI)	**p-value**	**Odds ratio* (95% CI)**	**p-value**	**Odds ratio* (95% CI)**	**p-value**
Education						
No/only primary	1.41 (1.02, 1.94)	0.038	1.00 (0.73, 1.37)	0.993	0.29 (0.19, 0.45)	<0.001
Secondary	1.35 (1.01, 1.80)	0.042	1.04 (0.78, 1.39)	0.784	0.47 (0.33, 0.65)	<0.001
Pre-University/ITE	1.05 (0.74, 1.48)	0.784	1.08 (0.75, 1.56)	0.679	0.55 (0.37, 0.83)	0.004
Degree/higher	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Monthly household income (USD)						
<1000	0.63 (0.45, 0.88)	0.007	0.70 (0.49, 0.99)	0.047	0.66 (0.45, 0.95)	0.026
1000-2999	0.67 (0.47, 0.94)	0.022	0.72 (0.50, 1.05)	0.089	1.03 (0.72, 1.47)	0.866
>=3000	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Regional income						
Low	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Middle	0.44 (0.34, 0.58)	<0.001	1.98 (1.5, 2.62)	<0.001	2.39 (1.59, 3.59)	<0.001
High	0.86 (0.66, 1.12)	0.263	2.70 (2.08, 3.5)	<0.001	3.29 (2.26, 4.77)	<0.001

*Adjusted additionally for age, sex, inpatient enrolment, NYHA class III/IV, BMI, heart rate, systolic blood pressure, history of CAD, atrial fibrillation, peripheral arterial disease, diabetes, chronic kidney disease and smoking

Explanatory notes: ACEi/ARB- angiotensin-converting-enzyme inhibitors/angiotensin receptor blocker; NYHA- New York Heart Association class; BMI – body mass index; CAD – coronary artery disease

Table 4: Associations of lower education status and lower household income with use of ACEi/ARBs and beta-blockers, by regional income

	ACEi/ARB		Beta-blocker	
	Odds ratio† (95% CI)	**p-value**	**Odds ratio† (95% CI)**	**p-value**
	No/ only primary education vs degree or higher education			
Low-income region	1.99 (1.44, 2.74)	<0.001	0.57 (0.43, 0.74)	<0.001
Middle-income region	0.63 (0.39, 1.01)	0.057	1.36 (0.80, 2.30)	0.256
High-income region	0.60 (0.42, 0.86)	0.005	0.29 (0.17, 0.48)	<0.001
	Household income <1000 vs >=3000			
Low-income region	1.08 (0.64, 1.82)	0.780	0.69 (0.43, 1.12)	0.131
Middle-income region	0.70 (0.44, 1.12)	0.136	1.13 (0.67, 1.89)	0.645
High-income region	0.47 (0.33, 0.67)	<0.001	0.39 (0.25, 0.60)	<0.001

†Adjusted additionally for age, sex, inpatient enrolment, NYHA class III/IV, BMI, heart rate, systolic blood pressure, history of CAD, atrial fibrillation, peripheral arterial disease, diabetes, chronic kidney disease and smoking

Explanatory notes: ACEi/ARB- angiotensin-converting-enzyme inhibitors/angiotensin receptor blocker; NYHA- New York Heart Association class; BMI – body mass index; CAD – coronary artery disease

Table 5: Association of SES variables with 1-year composite outcome adjusted for patient characteristics, comorbidities and processes of care (medications and device therapy)

	1-year composite outcome	
	Multivariable HR (95% CI)	**p-value**
Education		
No/only primary	1.48 (1.07, 2.04)	0.016
Secondary	1.27 (0.95, 1.71)	0.110
Pre-University/ITE	0.90 (0.62, 1.32)	0.597
Degree/higher	1.0 (ref)	
Monthly household income (USD)		
<1000	1.21 (0.87, 1.67)	0.253
1000-2999	0.90 (0.64, 1.26)	0.528
>=3000	1.0 (ref)	
Regional income		
Low	1.0 (ref)	
Middle	1.18 (0.89, 1.55)	0.252
High	1.34 (1.04, 1.73)	0.026
Age, years	1.00 (0.99, 1.01)	0.418
Women	1.18 (0.92, 1.51)	0.202
Enrolled as in-patient	1.57 (1.28, 1.91)	<0.001
NYHA Class III/IV	1.48 (1.21, 1.80)	<0.001
Body mass index, kg/m^2	0.97 (0.95, 0.99)	0.012
Heart rate, bpm	1.01 (1.00, 1.01)	0.002
Systolic blood pressure, mmHg	0.99 (0.99, 1.00)	0.005
Coronary artery disease	1.46 (1.19, 1.79)	<0.001
Atrial fibrillation	1.38 (1.11, 1.71)	0.003
PAVD	1.60 (1.08, 2.37)	0.019
Diabetes	1.34 (1.10, 1.62)	0.003
Chronic kidney disease	1.83 (1.50, 2.23)	<0.001
Ever smoked	1.56 (1.27, 1.92)	<0.001
ACEi/ARB	0.62 (0.51, 0.75)	<0.001
Beta-blockers	0.78 (0.63, 0.96)	0.021
MRA	1.17 (0.96, 1.42)	0.115
Device therapy	1.09 (0.84, 1.42)	0.496

Explanatory notes: NYHA- New York Heart Association class; PAVD – peripheral arterial/vascular disease; ACEi/ARB-angiotensin-converting-enzyme inhibitors/angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist

Table 6: Association of education and household income with 1-year composite outcome, stratified by regional income

	1-year composite outcome					
Socio-demographic factors	**Multivariable‡ HR (95% CI)**	**p value**	**Multivariable‡ HR (95% CI)**	**p value**	**Multivariable‡ HR (95% CI)**	**p value**
Stratified by regional income	**Low income**		**Middle income**		**High income**	
Education						
No/only primary	1.17 (0.72, 1.90)	0.536	0.80 (0.44, 1.45)	0.463	2.10 (1.36, 3.26)	0.001
Secondary	1.45 (0.95, 2.20)	0.084	1.02 (0.59, 1.75)	0.946	1.25 (0.80, 1.95)	0.332
Pre-University	1.08 (0.58, 2.01)	0.816	0.99 (0.54, 1.82)	0.966	0.73 (0.41, 1.31)	0.294
Degree or higher	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Monthly household income (USD)						
<1000	0.84 (0.45, 1.57)	0.581	0.91 (0.47, 1.75)	0.774	1.71 (1.15, 2.55)	0.008
1000-2999	0.59 (0.27, 1.28)	0.180	0.95 (0.47, 1.91)	0.883	0.97 (0.62, 1.51)	0.882
≥3000	1.00 (ref)		1.00 (ref)		1.00 (ref)	

‡Adjusted for age, sex, inpatient enrolment, NYHA class III/IV, BMI, heart rate, systolic blood pressure, history of CAD, atrial fibrillation, peripheral arterial disease, diabetes, chronic kidney disease, smoking, use of ACE-inhibitor or ARB, beta blocker and MRA.

Explanatory notes: NYHA- New York Heart Association class; BMI – body mass index; CAD – coronary artery disease; ACEi/ARB – angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MRA – mineralocorticoid receptor antagonists;

Figure 1

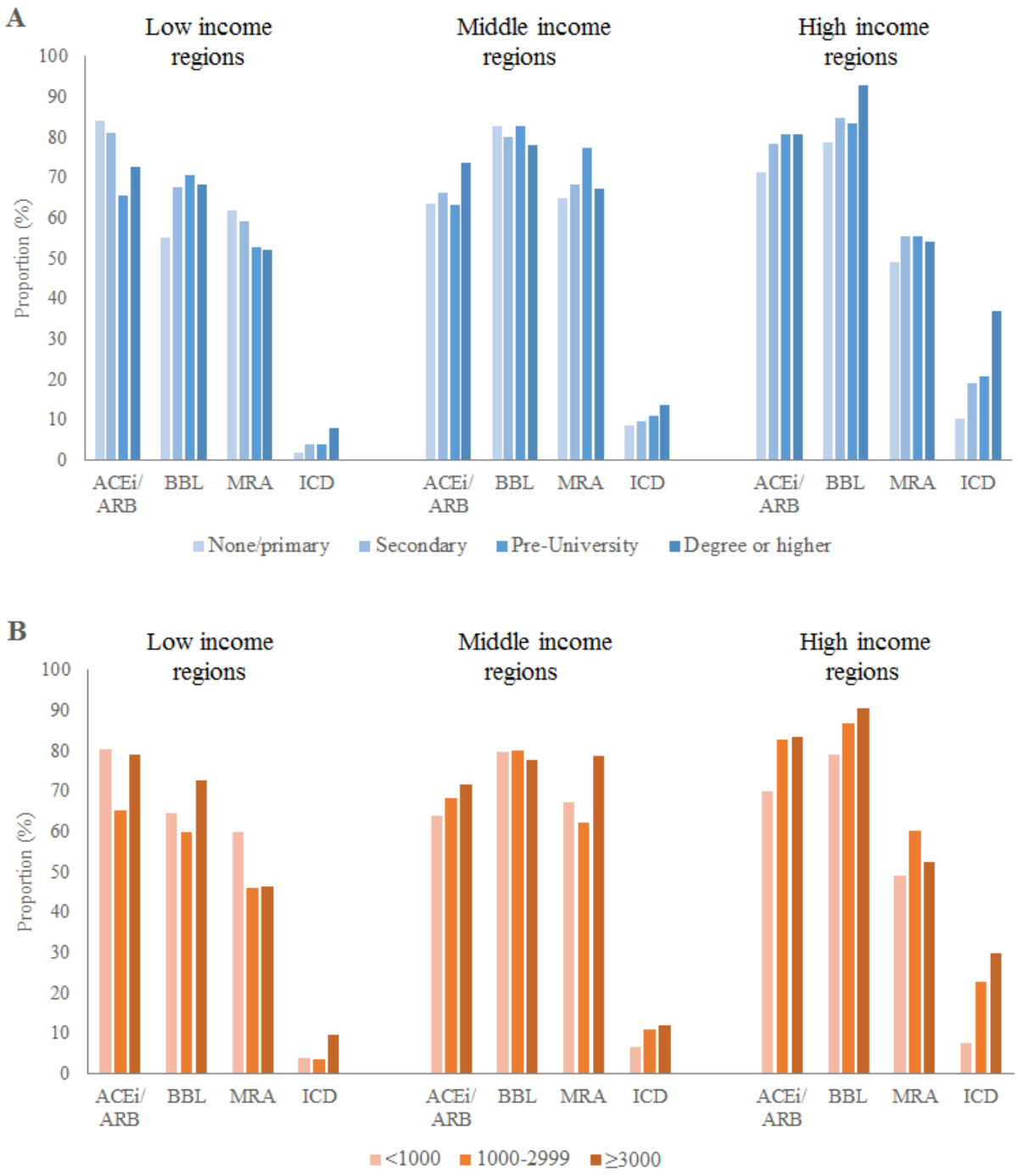
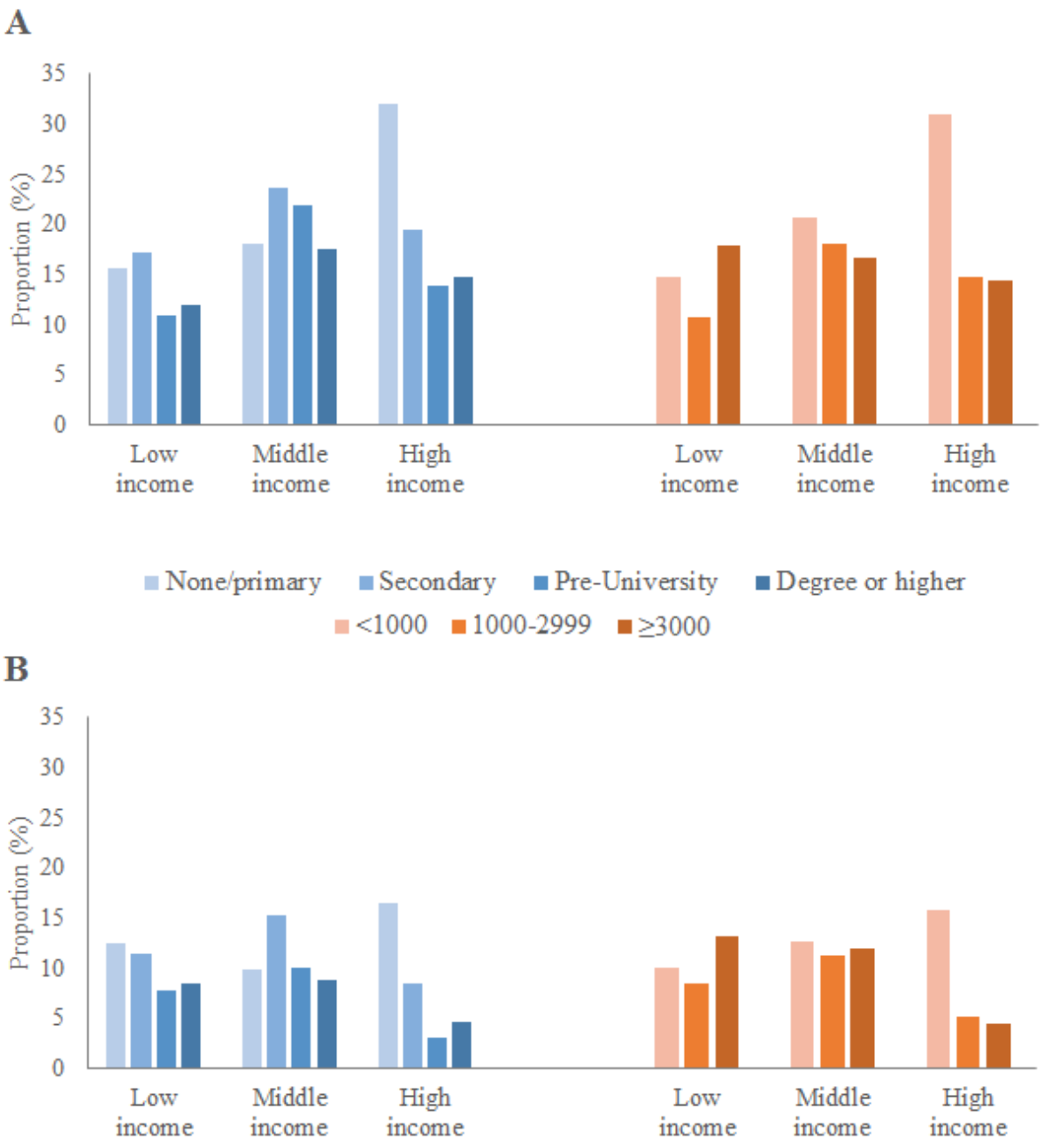

A
Low income regions
Middle income regions
High income regions
Proportion (%)
100
90
80
70
60
50
40
30
20
10
0
ACEi/ ARB
BBL
MRA
ICD
None/primary
Secondary
Pre-University
Degree or higher
B
Low income regions
Middle income regions
High income regions
Proportion (%)
<1000
1000-2999
≥3000

Figure 2


A
35
30
25
20
15
10
5
0
Proportion (%)
Low income
Middle income
High income
Low income
Middle income
High income
None/primary
Secondary
Pre-University
Degree or higher
<1000
1000-2999
≥3000
B
35
30
25
20
15
10
5
0
Proportion (%)
Low income
Middle income
High income
Low income
Middle income
High income

Appendix I

THE ASIAN-HF EXECUTIVE COMMITTEE

- Professor Carolyn S.P. Lam (as Principal Investigator), National Heart Centre Singapore, Duke-NUS Medical School, Singapore. Email: carolyn.lam@duke-nus.edu.sg
- Professor A. Mark Richards (as Chairman), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: mdcarthu@nus.edu.sg
- Professor Inder Anand (as Director, Publications Committee), University of Minnesota Medical School, VA Medical Center Minneapolis and San Diego, United States of America. Email: anand001@umn.edu
- Dr Chung-Lieh Hung, Mackay Memorial Hospital, Taipei, Taiwan. Email: jotaro3791@gmail.com
- Professor Lieng Hsi Ling (as Director, Echo Core Laboratory), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: lieng_hsi_ling@nuhs.edu.sg
- Dr Houng Bang Liew, Queen Elizabeth II Hospital, Clinical Research Center, Sabah, Malaysia. Email: hbliew22@gmail.com
- Dr Calambur Narasimhan, Care Hospital, Hyderabad, India. Email: calambur@hotmail.com
- Dr Tachapong Ngarmukos, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Email: tachaponis.nga@mahidol.ac.th
- Dr Sang Weon Park, SeJong General Hospital, Seoul, South Korea. Email: swparkmd@gmail.com
- Dr Eugenio Reyes, Manila Doctors Hospital, Manila, Philippines. Email: eugenereyes@yahoo.com
- Professor Bambang B. Siswanto, National Cardiovascular Center Universitas Indonesia, Jakarta, Indonesia. Email: bambbs@gmail.com
- Professor Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan. Email: wshimizu@nms.ac.jp
- Professor Shu Zhang, Fuwai Cardiovascular Hospital, Beijing, People's Republic of China. Email: zsfuwai@vip.163.com

COUNTRY AND SITE INVESTIGATORS

China

Fuwai Hospital: **Shu Zhang** (Country PI), Xiaohan Fan, Keping Chen. Ruijin Hospital, Shanghai Jiaotong university: Liqun Wu, Yucai Xie, Qi Jin, Tianyou Ling. The First Affiliated Hospital With Nanjing Medical University: Xinli Li, Fang Zhou, Yanli Zhou, Dongjie Xu, Haifeng Zhang. Zhongshan Hospital Fudan University: Yangang Su, Xueying Chen, Shengmei Qin, Jingfeng Wang, Xue Gong, Zhaodi Wu.

Hong Kong

The Chinese University of Hong Kong: **Cheuk Man Yu** (Country PI).

India

CARE Hospital: **Calambur Narasimhan** (Country PI), B K S Sastry, Arun Gopi, K Raghu, C Sridevi, Daljeet Kaur. Care Institute of Medical Sciences: Ajay Naik, Keyur Parikh, Anish Chandarana, Urmil Shah, Milan Chag, Hemang Baxi, Satya Gupta, Jyoti Bhatia, Vaishali Khakhkhar, Vineet Sankhla, Tejas Patel, Vipul Kapoor. Hero Dayanand Medical College Heart Institute: Gurpreet Singh Wander, Rohit Tandon. Medanta-The Medicity: Vijay Chopra, Manoj Kumar, Hatinder Jeet Singh Sethi, Rashmi Verma, Sanjay Mittal. Sir Ganga Ram Hospital: Jitendra Sawhney, Manish Kr. Sharma. Westfort Hi-Tech Hospital Ltd: Mohanan Padinhare Purayil.

Indonesia

Rumah Sakit Jantung dan Pembuluh Darah Harapan Kita: **Bambang Budi Siswanto** (Country PI). RS Dr Hasan Sadikin: Pintoko Tedjokusumo, Erwan Martanto, Erwinanto. R S Khusus Jantung Binawaluya: Muhammad Munawar, Jimmy Agung Pambudi. RS Siloam Karawaci: Antonia Lukito, Ingrid Pardede, Alvin Thengker, Vito Damay, Siska Suridanda Danny, Rarsari Surarso.

Japan

Nippon Medical School: **Wataru Shimizu** (Country PI), National Cerebral and Cardiovascular Center: Takashi Noda, Ikutaro Nakajima, Mitsuru Wada, Kohei Ishibashi. Kinki University Hospital Cardiovascular Center: Takashi Kurita, Ryoubun Yasuoka. Nippon Medical School Hospital: Kuniya Asai, Kohji Murai, Yoshiaki Kubota, Yuki Izumi.Toho University Omori Medical Center: Takanori Ikeda, Shinji Hisatake, Takayuki Kabuki, Shunsuke Kiuchi, Tokyo Women's Medical University: Nobuhisa Hagiwara, Atsushi Suzuki, Dr. Tsuyoshi Suzuki.

Korea

SeJong General Hospital: **Sang-Weon Park** (Country PI), Suk Keun Hong, SookJin Lee, Lim Dal Soo, Dong-Hyeok Kim. Korea University Anam Hospital: Jaemin Shim, Seong-Mi Park, Seung-Young Roh, Young Hoon Kim, Mina Kim, Jong-Il Choi. Korea University Guro Hospital: Jin Oh Na, Seung Woon Rha, Hong Seog Seo, Dong Joo Oh, Chang Gyu Park, Eung Ju Kim, Sunki Lee,
Severance Hospital, Yonsei University Health System: Boyoung Joung, Jae-Sun Uhm, Moon Hyoung Lee, In-Jeong Cho, Hui-Nam Park. Chonnam National University Hospital: Hyung-Wook Park, Jeong-Gwan Cho, Namsik Yoon, KiHong Lee, Kye Hun Kim. Korea University Ansan Hospital: Seong Hwan Kim.

Malaysia

Hospital Queen Elizabeth II: **Houng Bang Liew** (Country PI), Sahrin Saharudin, Boon Cong Beh, Yu Wei Lee, Chia How Yen, Mohd Khairi Othman, Amie-Anne Augustine, Mohd Hariz Mohd Asnawi, Roberto Angelo Mojolou, You Zhuan Tan, Aida Nurbaini Arbain, Chii Koh Wong. Institut Jantung Negara: Razali Omar, Azmee Mohd Ghazi, Surinder Kaur Khelae, David S.P. Chew, Lok Bin Yap, Azlan Hussin, Zulkeflee Muhammad, Mohd. Ghazi Azmee. University Malaya Medical Centre: Imran Zainal Abidin, Ahmad Syadi Bin Mahmood Zhudi, Nor Ashikin Md Sari, Ganiga Srinivasaiah Sridhar, Ahmad Syadi Mahmood Zuhdi. Muhammad Dzafir Ismail. Sarawak General Hospital Heart Centre: Tiong Kiam Ong, Yee Ling Cham, Ning Zan Khiew, Asri Bin Said, Alan Yean Yip Fong, Nor Hanim Mohd Amin, Keong Chua Seng, Sian Kong Tan, Kuan Leong Yew.

Philippines

Manila Doctors Hospital: **Eugenio Reyes** (Country PI), Jones Santos, Allan Lim. Makati Medical Center: Raul Lapitan, Ryan Andal, Philippine Heart Center: Eleanor Lopez.

Singapore

National Heart Centre Singapore: **Carolyn S.P. Lam** (Country PI), Kheng Leng David Sim, Boon Yew Tan, Choon Pin Lim, Louis L.Y. Teo, Laura L.H. Chan. National University Heart Centre: Lieng Hsi Ling, Ping Chai, Ching Chiew Raymond Wong, Kian Keong Poh, Tan Tock Seng Hospital: Poh Shuan Daniel Yeo, Evelyn M. Lee, Seet Yong Loh, Min Er Ching, Deanna Z.L. Khoo, Min Sen Yew, Wenjie Huang. Changi General Hospital-Parent: Kui Toh Gerard Leong, Jia Hao Jason See, Yaozong Benji Lim, Svenszeat Tan, Colin Yeo, Siang Chew Chai. Singapore General Hospital-Parent: Fazlur Rehman Jaufeerally, Haresh Tulsidas, Than Aung. Khoo Teck Puat Hospital: Hean Yee Ong, Lee Fong Ling, Dinna Kar Nee Soon

Taiwan

Mackay Memorial Hospital, Taipei, Taiwan: **Chung-Lieh Hung** (Country PI), Hung-I Yeh,Jen-Yuan Kuo, Chih-Hsuan Yen. National Taiwan University Hospital: Juey-Jen Hwang, Kuo-Liong Chien, Ta-Chen Su, Lian-Yu Lin, Jyh-Ming Juang, Yen-Hung Lin, Fu-Tien Chiang, Jiunn-Lee Lin, Yi-Lwun Ho, Chii-Ming Lee, Po-Chih Lin, Chi-Sheng Hung, Sheng-Nan Chang, Jou-Wei Lin, Chih-Neng Hsu. Taipei Veterans General Hospital: Wen-Chung Yu, Tze-Fan Chao, Shih-Hsien Sung, Kang-Ling Wang, Hsin-Bang Leu, Yenn-Jiang Lin, Shih-Lin Chang, Po-Hsun Huang, Li-Wei Lo, Cheng-Hsueh Wu. China Medical University Hospital: Hsin-Yueh Liang, Shih-Sheng Chang, Lien-Cheng Hsiao, Yu-Chen Wang, Chiung-Ray Lu, Hung-Pin Wu, Yen-Nien Lin, Ke-Wei Chen, Ping-Han Lo, Chung-Ho Hsu, Li-Chuan Hsieh.

Thailand

Ramathibodi Hospital: **Tachapong Ngarmukos** (Country PI), Mann Chandavimol, Teerapat Yingchoncharoen, Prasart Laothavorn. Phramongkutklao Hospital:Waraporn Tiyanon. Maharaj Nakorn Chiang Mai Hospital: Wanwarang Wongcharoen, Arintaya Phrommintikul.