Association between body surface area and prescribed doses of guideline-directed medications among international patients with heart failure and reduced ejection fraction

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Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.1648

RESEARCH LETTER

doi:10.1002/ejhf.1648

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Clinical practice guidelines advocate evidence-based heart failure (HF) medications at guideline-directed doses (GDD) for patients with HF and reduced ejection fraction (HFrEF).[1] Despite standardized GDD for all patients with HFrEF, striking differences in doses of HF medications are prescribed in real-world clinical practice; differences that are not fully explained by patient intolerance or known contraindications to up-titration. Dosages are particularly low in HFrEF from Asian countries,[2] which has been postulated because Asian patients have smaller body size and greater sensitivity to drugs, thus requiring reduced dosages of medications.[2,3] However, data to support this hypothesis are limited. There are currently no recommendations for dose adjustment based on body size. The combined cohort[4] of HF patients with left ventricular ejection fraction ≤35% from ASIAN-HF[5] and HF-ACTION[6] was used to address the aims in our study. We first describe the usage patterns for HFrEF therapy in regions across Asia, United States (US), Canada, and France. Secondly, we evaluate the association of body surface area (BSA) and medication dose. Finally, we determine whether region affects the association between BSA and medication doses.

Doses of HF medications [angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB), β-blockers, diuretics] at baseline were standardized using equivalents of carvedilol for β-blockers and lisinopril for ACEi.[7] Attainment of GDD (yes/no) for β-blockers was defined as ≥50 mg carvedilol and ACEi as ≥20 mg lisinopril equivalents. BSA was calculated according to the Mosteller formula [weight (kg) × height (cm)/3600]$^{1/2}$. Stepwise forward regression models were used to examine the association between BSA with maximum prescribed doses (as a continuous variable) of β-blockers and ACEi, in addition to contributing factors [heart rate, systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR) and other confounders]. Interaction of BSA with region (US, Canada, France, Northeast Asia, South Asia, and Southeast Asia) for the outcome of GDD was tested. Ethics approvals were obtained from institutional review committee of each participating centre, which conform to the Declaration of Helsinki.

Among a combined cohort of 6683 patients with HFrEF (mean age 59 ± 13 years, 23% women), 4543 (68%) were Asian and 2140 (32%) were White or Black (non-Asian) from North America/Europe. Asians vs. non-Asians were similar in age, New York Heart Association class III/IV (36%), prevalence of coronary artery disease (51%) and chronic kidney disease (45%), but were more likely to have diabetes (42% vs. 32%, $P < 0.001$) and less likely to have hypertension (51% vs. 59%, $P < 0.001$) (online supplementary *Table S1*). Compared to non-Asians, Asians were less likely to be prescribed β-blockers (78% vs. 95%) and ACEi/ARBs (76% vs. 94%). Median daily carvedilol and lisinopril dose equivalents in Asians were half of those in non-Asians [12.5 (interquartile range-IQR 6.25–25) mg vs. 25 (IQR 13–50) mg and 10 (IQR 5–20) mg vs. 20 (IQR 10–40) mg, respectively]. However, furosemide daily dosages were similar (40 mg) in both sub-cohorts. There was significant variability in doses across regions (*Table 1*), with lowest mean doses in East Asia and South Asia vs. other regions. Among Asians, only 14% achieved GDD for β-blockers, 22% for ACEi compared to 37% and 40%, respectively, in non-Asians.

In general, Asians had lower BSA compared to non-Asians (1.74 ± 0.22 vs. 2.11 ± 0.29 m^2) (*Table 1*). BSA was strongly related to medication dose [β-coefficients per unit increment = 21.51 (standard error-SE 0.909) for β-blockers;14.43 (SE 0.89) for ACEi; $P < 0.001$], as well as odds of attaining GDD [odds ratio per unit increase in BSA = 9.74, 95% confidence interval (CI) 7.89–12.02 for β-blockers and 4.64, 95% CI 3.78–5.70 for ACEi; $P < 0.001$]. These associations persisted even after multivariable adjustment.

In the multivariable models, geographic region showed strong associations with doses of β-blockers and ACEi, independent of BSA, SBP, heart rate, eGFR, and co-morbidities. Furthermore, region modified the association of BSA with β-blocker ($P_{interaction} < 0.001$) and with ACEi doses ($P_{interaction} = 0.008$). When stratified by region (*Figure 1*), BSA was positively associated with β-blocker dose in the US, South Asia and Southeast Asia (all $P \leq 0.035$), but only in the US (β-coefficient 7.41, SE 2.2, $P < 0.001$) for ACEi dose. Within each region, dosages were influenced by other factors, e.g. SBP, eGFR and β-blocker dose for ACEi dose (all $P \leq 0.001$) (*Figure 1*). Higher doses of β-blockers and ACEi showed an inverse graded correlation with crude 1-year mortality (all $P < 0.001$).

Despite the widely held perception that Asian patients need lower dosages of medications, studies comparing dosage patterns of HF medications in Asians vs. non-Asians are scarce.[2,8,9] In our analysis, we found larger body size was associated with maximum prescribed dosage; however, geographic region was a strong modifier of that association. Notably, while healthcare providers might be less inclined to titrate β-blocker and ACEi doses in various regions based on BSA of patients, our findings suggest that differences in patients' risk factor profiles (SBP, heart rate, eGFR) and regional practice, rather than body size *per se*, may influence HF dosage patterns.

Other factors may contribute to lower doses in Asians. Emerging studies suggest that persistent cough is a common side-effect associated with ACEi among Asian ethnicities,[3] with incidence of ACEi-induced persistent cough occurring in one-third of patients in a multi-ethnic Asian cohort (particularly Chinese).[3] Genetic differences could partly explain the variation in dosing patterns of ACEi observed across the regions and multi-ethnicities.[10,11] For β-blockers, low doses of carvedilol are commonly prescribed in Japan,[2] following findings of lower doses being tested in the Japanese randomized, placebo-controlled double-blind MUCHA trial.[9] Enhanced enrolment of patients from different regions in ongoing trials/registries will therefore be necessary to better

Table 1 Baseline characteristics by geographical region

	Geographical region						
	USA	**Canada**	**France**	**Northeast Asia**	**South Asia**	**Southeast Asia**	***P*-value**
n	1884	181	75	1303	1321	1919	
Demographics							
Age, years	58.8 (12.9)	61.9 (10.3)	56.8 (9.1)	61.4 (14.7)	57.5 (12.4)	58.7 (12.0)	<0.001
Female sex	534 (28.3%)	29 (16.0%)	16 (21.3%)	312 (23.9%)	321 (24.3%)	319 (16.6%)	<0.001
Ethnicity							
Black	662 (35.1%)	7 (3.9%)	5 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
White	1094 (58.1%)	160 (88.4%)	70 (93.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Chinese	0 (0.0%)	0 (0.0%)	0 (0.0%)	610 (46.8%)	0 (0.0%)	687 (35.8%)	
Malay	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	718 (37.4%)	
Indian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1320 (99.9%)	193 (10.1%)	
Japanese/Korean	0 (0.0%)	0 (0.0%)	0 (0.0%)	691 (53.0%)	0 (0.0%)	1 (0.1%)	
Other	128 (6.8%)	14 (7.7%)	0 (0.0%)	2 (0.2%)	1 (0.1%)	320 (16.7%)	
Clinical characteristics							
NYHA class III/IV	725 (38.5%)	55 (30.4%)	19 (25.3%)	574 (49.5%)	429 (37.7%)	466 (25.5%)	<0.001
Height, m	1.73 (0.10)	1.72 (0.10)	1.70 (0.08)	1.65 (0.09)	1.65 (0.09)	1.63 (0.09)	<0.001
Weight, kg	94.5 (23.8)	88.8 (19.8)	78.1 (16.5)	65.1 (15.5)	67.6 (13.7)	68.7 (17.1)	<0.001
Body mass index, kg/m^2	31.4 (7.3)	30.1 (5.9)	26.8 (4.5)	23.7 (4.5)	25.0 (4.8)	25.6 (5.7)	<0.001
Body surface area, m^2	2.12 (0.29)	2.05 (0.26)	1.91 (0.23)	1.72 (0.23)	1.75 (0.20)	1.76 (0.24)	<0.001
LV ejection fraction, %	24.0 (6.3)	23.2 (5.4)	23.9 (5.5)	26.4 (6.1)	27.4 (5.4)	24.1 (6.4)	<0.001
Ischaemic aetiology of HF	967 (51.3%)	111 (61.3%)	41 (54.7%)	375 (31.1%)	485 (38.6%)	1215 (68.0%)	<0.001
Systolic BP, mmHg	114.2 (18.3)	113.5 (19.5)	104.4 (13.4)	115.4 (18.9)	115.2 (18.2)	120.7 (20.8)	<0.001
Diastolic BP, mmHg	70.7 (11.3)	68.6 (11.4)	65.6 (9.4)	70.7 (13.0)	73.5 (10.8)	72.6 (13.1)	<0.001
Hypotension	277 (14.7%)	25 (13.8%)	6 (8.0%)	236 (18.3%)	64 (4.9%)	271 (14.4%)	<0.001
Heart rate, bpm	71.4 (11.4)	67.9 (11.7)	68.9 (12.7)	79.3 (16.7)	81.6 (15.4)	79.5 (15.8)	<0.001
Bradycardia	181 (9.6%)	39 (21.7%)	15 (29.0%)	82 (6.4%)	54 (5.1%)	118 (6.3%)	<0.001
eGFR, mL/min/1.73 m^2	63.8 (23.3)	60.9 (19.7)	57.5 (22.6)	67.2 (28.3)	72.5 (32.7)	60.3 (26.0)	<0.001
Chronic kidney disease	758 (45.1%)	85 (48.3%)	33 (54.1%)	465 (40.0%)	311 (36.3%)	823 (52.1%)	<0.001
Medical history							
Coronary artery disease	965 (51.2%)	104 (57.5%)	44 (58.7%)	466 (35.9%)	682 (51.6%)	1111 (58.8%)	<0.001
Hypertension	1171 (62.5%)	84 (47.5%)	9 (12.0%)	604 (46.5%)	491 (37.2%)	1194 (63.3%)	<0.001
Diabetes	614 (32.6%)	59 (32.6%)	11 (14.7%)	443 (34.0%)	518 (39.2%)	964 (50.2%)	<0.001
Atrial fibrillation	402 (21.3%)	42 (23.2%)	6 (8.0%)	401 (30.9%)	51 (3.9%)	323 (17.1%)	<0.001
Prior stroke	204 (10.8%)	18 (9.9%)	3 (4.0%)	99 (7.6%)	24 (1.8%)	165 (8.7%)	<0.001
Peripheral vascular disease	126 (6.7%)	15 (8.3%)	2 (2.7%)	51 (3.9%)	18 (1.4%)	73 (3.9%)	<0.001
Medications							
ACEi	1390 (73.8%)	142 (78.5%)	61 (81.3%)	638 (49.3%)	573 (44.2%)	1077 (58.3%)	<0.001
ACEi dose[a], mg	20 (10, 40)	30 (20, 40)	20 (10, 32)	10 (5, 12.5)	20 (10, 40)	12.5 (10, 25)	<0.001
ACEi or ARB	1764 (93.6%)	177 (97.8%)	74 (98.7%)	950 (73.5%)	976 (75.3%)	1449 (78.5%)	<0.001
β-blocker	1780 (94.5%)	172 (95.0%)	71 (94.7%)	1069 (82.7%)	863 (66.6%)	1539 (83.3%)	<0.001
β-blocker dose[b], mg	25 (13, 50)	31.0 (25, 50)	40 (20, 50)	12.5 (6.3, 25)	12.5 (6.3, 25)	18.8 (12.5, 25)	<0.001
Loop diuretic	1462 (77.6%)	152 (84.0%)	65 (86.7%)	1013 (78.3%)	1078 (83.2%)	1618 (87.6%)	<0.001
Loop diuretic dose[c], mg	40 (40, 80)	40 (20, 80)	40 (20, 40)	40 (20, 80)	40 (20, 40)	40 (40, 80)	<0.001
Clinical outcomes							
Death at 1 year	99 (5.3%)	9 (5.0%)	0 (0.0%)	107 (8.8%)	98 (8.1%)	226 (13.8%)	<0.001

Categorical variables were analysed as frequencies (%) using the Chi-square test. Continuous variables were compared by *t*-test and presented as mean ± standard deviation. Two-tailed *P*-value <0.05 was considered significant.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association.

Geographic regions were defined according to the United Nations classification as follows: Northeast Asia – South Korea, Japan, Taiwan, Hong Kong and China; South Asia – India; Southeast Asia – Thailand, Malaysia, Philippines, Indonesia and Singapore.

[a]Lisinopril equivalent.

[b]Carvedilol equivalent.

[c]Furosemide equivalent.

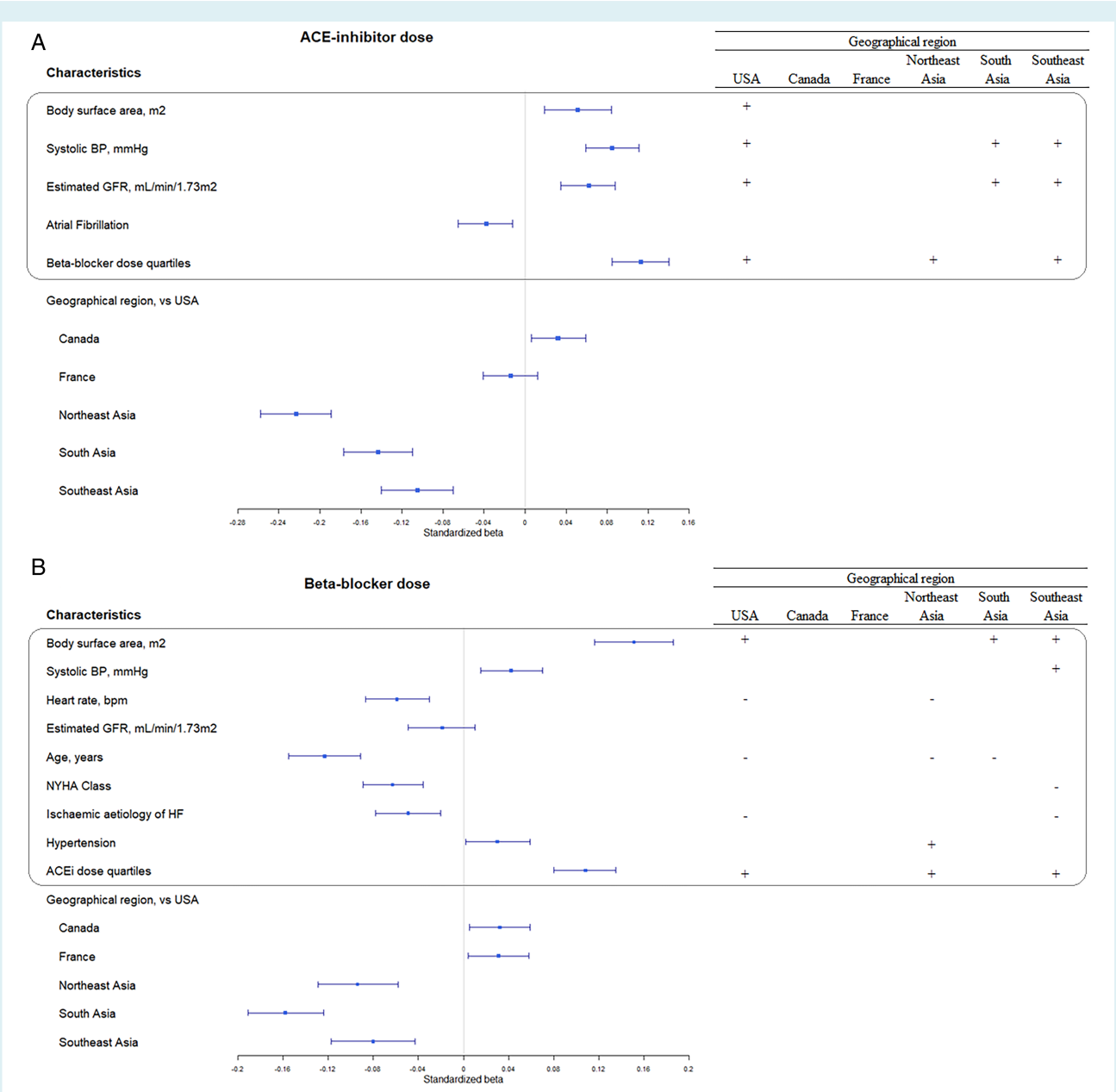

Figure 1 Adjusted association of body surface area with (*A*) angiotensin-converting enzyme inhibitor (ACEi) and (*B*) β-blocker dosage, in the overall cohort and by geographical region. ACEi dose in lisinopril equivalent, β-blocker dose in carvedilol equivalent. [+] and [−] indicate significant positive and negative associations with ACEi and β-blocker doses in respective geographical regions. BP, blood pressure; GFR, glomerular filtration rate; HF, heart failure; NYHA, New York Heart Association.

understand the true optimal dosing benefits of HF medications in real-world populations.

Limitations to our study include selection bias inherent in combining an observational registry with a clinical trial population (as a benchmark for best practices). There was incomplete categorization of ARB and mineralocorticoid receptor antagonist dosages, hence its exclusion from the analysis. As such, conclusions between medication dosages and patient outcomes cannot be made.

In summary, we found significant regional variation in HF medication dosages among HFrEF patients, with lower doses being prescribed in Asia. While body size was related to HF medication dosages, geographic region modified this association and remained a strong independent predictor of prescribed doses. Greater understanding of the regional differences in dosage patterns and their association with patient outcomes is needed.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison of characteristics in Asian and non-Asian patients.

Acknowledgements

We thank all investigators and participants of HF-ACTION and ASIAN-HF for their contribution.

Funding

The ASIAN-HF study is supported by grants from Boston Scientific Investigator Sponsored Research Program, National Medical Research Council of Singapore, A*STAR Biomedical Research Council ATTRaCT program, and Bayer. The HF-ACTION trial was supported by grants from the National Heart, Lung and Blood Institute (USA) (NCT00047437).

Conflict of interest: A.S. is supported by the Alberta Innovates Health Solution Fellowship and has received research and personal support from Takeda, Boehringer Ingelheim, BMS/Pfizer, Merck, Akcea Pharmaceutical, and Roche Diagnostics. A.M.R. has received research support from Boston Scientific, Bayer, AstraZeneca, Medtronic, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics; and has consulted for Bayer, Novartis, Merck, AstraZeneca, Roche Diagnostics. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council Singapore; has received research support from Boston Scientific, Medtronic, and Vifor Pharma; and has consulted for Bayer, Novartis, Takeda, Merck, AstraZeneca, Janssen Research & Development, LLC and Menarini; has served on the Clinical Endpoint Committee for DC Devices. The other authors have nothing to disclose.

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References

1. 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 J Heart Fail* 2016;**18**:891–975.
2. Teng TH, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, Wander GS, Yap JJ, MacDonald MR, Xu CF, Shimizu W, Richards AM, Voors A, Lam CS; ASIAN-HF Investigators. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: a cohort study. *Lancet Glob Health* 2018;**6**:e1008–e1018.
3. Ng LP, Goh PS. Incidence of discontinuation of angiotensin-converting enzyme inhibitors due to cough, in a primary healthcare Centre in Singapore. *Singapore Med J* 2014;**55**:146–149.
4. Cooper LB, Yap J, Tay WT, Teng TH, MacDonald M, Anand I, Sharma A, O'Connor CM, Kraus WE, Mentz RJ, CS L; HF-ACTION and ASIAN-HF Investigators. Multi-ethnic comparisons of diabetes in heart failure with reduced ejection fraction: insights from the HF-ACTION trial and the ASIAN-HF registry. *Eur J Heart Fail* 2018;**20**:1281–1289.
5. Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. 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.
6. Felker GM, Whellan D, Kraus WE, Clare R, Zannad F, Donahue M, Adams K, McKelvie R, Pina IL, O'Connor CM; HF-ACTION Investigators. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. *Am Heart J* 2009;**158**:S37–S44.
7. Fiuzat M, Neely ML, Starr AZ, Kraus WE, Felker GM, Donahue M, Adams K, Pina IL, Whellan D, O'Connor CM. Association between adrenergic receptor genotypes and beta-blocker dose in heart failure patients: analysis from the HF-ACTION DNA substudy. *Eur J Heart Fail* 2013;**15**:258–266.
8. Kitakaze M, Sarai N, Ando H, Sakamoto T, Nakajima H. Safety and tolerability of once-daily controlled-release carvedilol 10-80 mg in Japanese patients with chronic heart failure. *Circ J* 2012;**76**:668–674.
9. Hori M, Sasayama S, Kitabatake A, Toyo-oka T, Handa S, Yokoyama M, Matsuzaki M, Takeshita A, Origasa H, Matsui K, Hosoda S; MUCHA Investigators. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *Am Heart J* 2004;**147**:324–330.
10. Lee EJ. Population genetics of the angiotensin-converting enzyme in Chinese. *Br J Clin Pharmacol* 1994;**37**:212–214.
11. Johnson JA. Ethnic differences in cardiovascular drug response: potential contribution of pharmacogenetics. *Circulation* 2008;**118**:1383–1393.

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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.