Prescription patterns of anti-diabetic medications and clinical outcomes in Asian patients with heart failure and diabetes mellitus

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Type 2 diabetes mellitus (DM) is highly prevalent among Asian patients with heart failure (HF)[1] and Asians develop HF and DM almost a decade earlier[2,3] than their Western counterparts. Co-existence of both conditions carry worse prognosis than either alone,[1] with increased rates of progression to DM-related complications. Anti-diabetic medications are important for glycaemic control. While some may worsen HF, some newer agents may improve cardiovascular outcomes. Prospective multinational data on concomitant pharmacological management of DM and HF are scarce. We investigated patients with DM and HF with reduced ejection fraction (HFrEF) enrolled in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry[2] to assess the prescription patterns of anti-diabetic and anti-HF medications and to determine the association of anti-diabetic medications with 1-year all-cause mortality or HF hospitalisation.

The ASIAN-HF is a prospective registry comprising 5276 patients with HFrEF[2] recruited across 11 regions and three geographic blocs (Northeast Asia, South Asia, and Southeast Asia) between October 2012 and December 2015. DM was defined by documented diagnosis of DM from patients' medical records, self-reported history of DM, or use of anti-diabetic medications. Key therapeutic classes of anti-diabetic medications included: insulin, metformin, sulfonylureas (SUs) and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Patients were followed up for 1 year from baseline visit. We performed Cox regression accounting for indication bias with propensity score adjustment, where variables included in the propensity score were age, sex, body mass index, ejection fraction (EF), New York Heart Association classification, systolic blood pressure, aetiology of HF, co-morbidities (e.g. atrial fibrillation, prior stroke), and geographical regions. Ethics approvals were obtained from the institutional review committee of each participating centre, which conform to the Declaration of Helsinki.

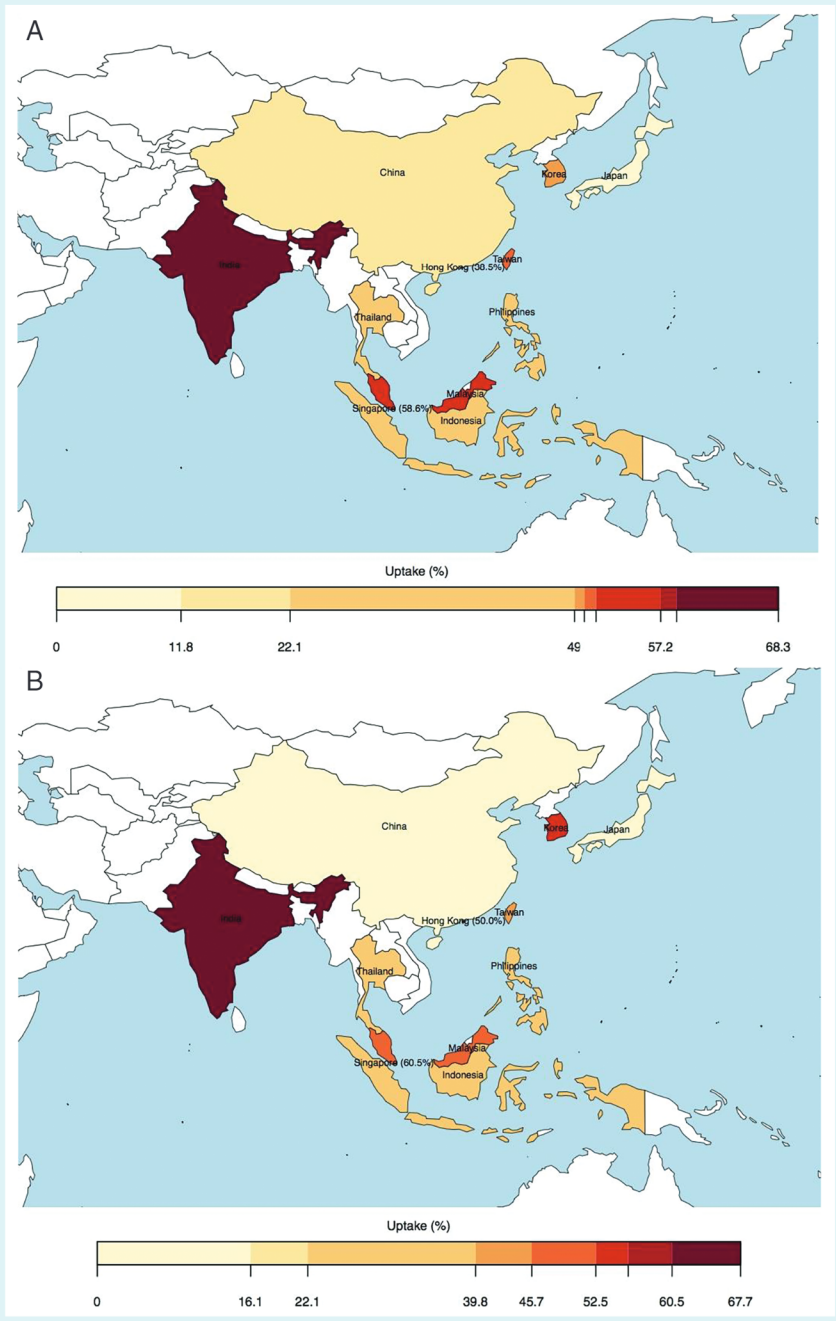

Figure 1 Regional uptake of metformin (*A*), sulfonylureas (*B*), insulin (*C*) and dipeptidyl peptidase-4 inhibitors (*D*) in Asia.

Diabetes mellitus was highly prevalent among 2102 (40%) of 5276 patients with HFrEF (mean age: 61 ± 11 years, 78% men,

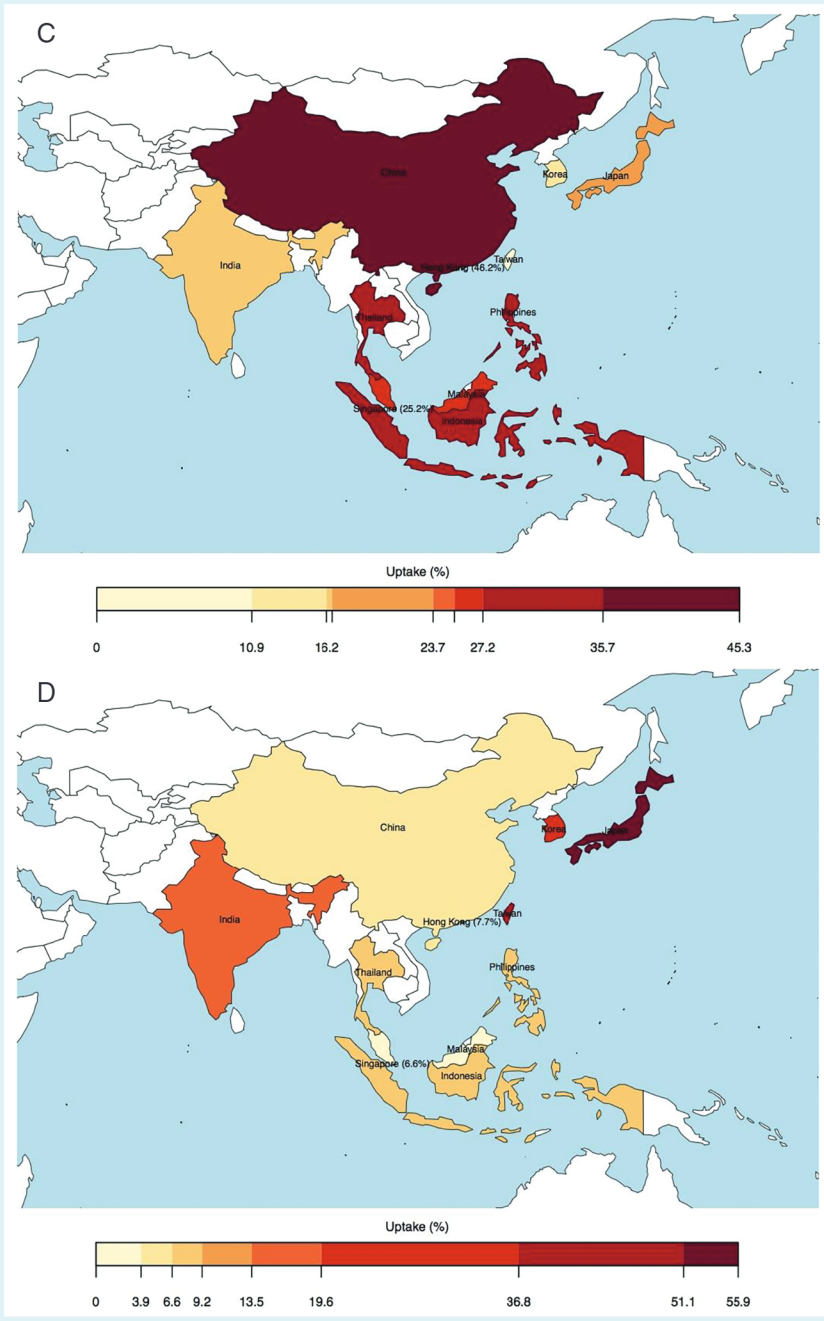

Figure 1 Continued.

mean left ventricular EF 27 ± 7%). Average duration of DM was 10 ± 8 years. Patients on (vs. no) insulin therapy had longer duration of DM (14 ± 9 vs. 9 ± 8 years, $P < 0.01$). About two-thirds of patients ($n = 1445$, 69%) were on at least one anti-diabetic medication; the most commonly prescribed agents being: metformin (54%) and SUs (53%); followed by insulin (24%) and DPP4 inhibitors (17%). Thiazolidinediones with known risk of worsening HF were rarely prescribed (0.4%). Half of the patients on anti-diabetic medications received monotherapy, while 527 (37%) were on dual therapy. Wide geographical variations in the prescribing patterns of anti-diabetic medications across Asia were observed (*Figure 1*).

Patients with (vs. without) DM were less likely to be prescribed renin–angiotensin–aldosterone system inhibitors (RAASi, 74% vs. 77%, $P = 0.02$) and mineralocorticoid receptor antagonists (MRAs, 55% vs. 61%, $P < 0.01$). Among 1761 patients with DM and available serum creatinine levels, 950 (54%) had chronic kidney disease (CKD, defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2) with 699 patients in stage 3 and 251 patients in stages 4–5. Patients with (vs. no) CKD were less likely to be treated with metformin (24% vs. 49%), RAASi (65% vs. 82%) and MRAs (45% vs. 64%) (all $P < 0.01$). In contrast, uptake of SUs (34% vs. 37%, $P = 0.12$), DPP-4 inhibitors (14% vs. 11%, $P = 0.09$) or beta-blockers (78% vs. 82%, $P = 0.07$) were similar. Among patients without renal contraindications to metformin therapy, 54% were not taking metformin.

Metformin use was low in Japan (11.8%) and China (14.5%) despite lower prevalence of CKD in these countries. In contrast, DPP-4 inhibitors were widely used in Northeast Asia (particularly Japan and Taiwan), with saxagliptin accounting for 50% of DPP-4 inhibitors prescribed. Patients treated with (vs. without) metformin were more likely to receive evidence-based medications for HF (all $P < 0.01$) (*Table 1*).

Among 4694 (89%) patients with HFrEF and complete follow-up, the 1-year composite outcome occurred in 26% and 17% of patients with and without DM ($P < 0.01$), respectively. In unadjusted analysis, only metformin therapy was associated with reduced risk of the composite outcome (23% vs. 28%, $P = 0.02$). After adjustment for indication bias, a trend towards reduced risk of the composite outcome was observed with metformin therapy [propensity score adjusted hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.64–1.01]. No significant risk reduction in outcomes was associated with other anti-diabetic medications.

Previous observational studies have suggested that as compared to metformin, SUs are associated with increased risk of both cardiovascular events and total mortality.[4] It is noteworthy that SUs were as commonly prescribed as metformin in our HF population, despite the lack of clear benefit for SUs in patients with concomitant DM and HF. Our findings suggest that metformin (as opposed to SUs) might be associated with improved outcomes and hence should be considered as first-line therapy unless contraindicated, in accordance with current guideline recommendations.[5]

Reasons for the infrequent use of metformin in Japan and China were not assessed. In Japan, this could be related to mandated lactate measurements in elderly patients on high-dose metformin.[6] Although elderly

Table 1 Baseline characteristics associated with prescription of individual anti-diabetic medications

Characteristics	No anti-diabetic medications ($n = 657$)	On anti-diabetic medications ($n = 1445$)	*P*-value	No metformin ($n = 1326$)	On metformin ($n = 776$)	*P*-value	No sulfonylureas ($n = 1334$)	On sulfonylureas ($n = 768$)	*P*-value
Age (years)	62 ± 11	61 ± 11	<0.01	62 ± 11	60 ± 11	<0.01	62 ± 11	61 ± 11	0.02
Male sex	523 (80)	1132 (78)	0.51	1037 (78)	618 (80)	0.44	1035 (78)	620 (81)	0.09
Inpatient enrolment	325 (50)	679 (47)	0.30	706 (53)	298 (38)	<0.01	690 (52)	314 (41)	<0.01
BMI (kg/m^2)	25 ± 5	26 ± 5	<0.01	25 ± 5	26 ± 5	<0.01	25 ± 5	26 ± 5	0.11
Heart rate (b.p.m.)	81 ± 17	80 ± 15	0.61	80 ± 17	81 ± 15	0.24	80 ± 17	80 ± 15	0.86
SBP (mmHg)	120 ± 20	121 ± 20	0.46	121 ± 21	120 ± 19	0.10	121 ± 20	121 ± 21	0.73
DBP (mmHg)	73 ± 13	72 ± 12	0.60	72 ± 13	73 ± 12	0.37	72 ± 13	72 ± 12	0.77
Ischaemic HF	480 (73)	1063 (74)	0.77	981 (74)	562 (73)	0.45	977 (73)	566 (74)	0.80
LVEF (%)	28 ± 7	27 ± 7	0.51	28 ± 7	27 ± 7	0.04	28 ± 7	27 ± 7	0.30
NYHA class III–IV	227 (39.1)	449 (33.9)	0.03	454 (38)	222 (31)	<0.01	455 (38)	221 (31)	<0.01
QRS (ms)	116 ± 33	113 ± 31	0.14	116 ± 32	111 ± 30	<0.01	113 ± 32	114 ± 31	0.67
Co-morbidities									
CAD	432 (66)	922 (64)	0.41	865 (65)	489 (63)	0.31	868 (65)	486 (63)	0.42
Atrial fibrillation	99 (15)	242 (17)	0.33	226 (17)	115 (15)	0.18	220 (17)	121 (16)	0.66
Hypertension	416 (63)	991 (69)	0.02	897 (68)	510 (66)	0.40	890 (67)	517 (68)	0.73
CKD	314 (56)	636 (53)	0.17	723 (63)	227 (37)	<0.01	632 (55)	318 (52)	0.12
HF medications									
RAASi	444 (68)	1102 (76)	<0.01	892 (67)	654 (84)	<0.01	935 (70)	611 (80)	<0.01
Beta-blockers	482 (74)	1174 (81)	<0.01	1018 (77)	638 (82)	<0.01	1029 (77)	627 (82)	0.02
MRA	348 (53)	810 (56)	0.20	701 (53)	457 (59)	<0.01	734 (55)	424 (55)	0.95
Diuretics	548 (84)	1260 (87)	0.03	1131 (85)	677 (87)	0.23	1125 (84)	683 (89)	<0.01

Values are expressed as number (%), or mean ± standard deviation.
BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAASi, renin–angiotensin–aldosterone system inhibitors; SBP, systolic blood pressure.
Missingness: NYHA class (10.2%); CKD (16.4%).

patients may be at higher risk for lactic acidosis, this risk is related more to co-morbidities which contraindicate metformin use rather than age.[7] A systematic review of 347 comparative trials and cohort studies in DM also found no evidence of metformin being associated with increased risk of lactic acidosis vs. other anti-diabetic medications.[8]

This study provides novel insight into the prescribing pattern across a vast geography of Asian patients with HF and DM. However, there are several limitations. Reasons for choice of anti-diabetic medications were not obtained. Being an observational study, causality cannot be inferred. Glycated haemoglobin measurements were lacking, which might influence anti-diabetic medication choices and outcomes. However, after adjusting for microvascular complications as surrogate markers of glycaemic control, metformin was still associated with a trend towards reduced risk for the primary composite outcome (propensity score adjusted HR 0.81, 95% CI 0.65–1.02). Finally, information pertaining to newer agents (i.e. sodium–glucose co-transporter-2 inhibitors), which pre-date the enrolment of patients in ASIAN-HF, was lacking.

In conclusion, prevalence of DM was high (40%) among Asian patients with HFrEF. Prescribing patterns for DM medications varied across Asia. Despite guideline recommendations and evidence that metformin was related to improved outcomes in patients with HF, metformin was used only in about half of the patients even in absence of renal contraindications. In contrast, SUs and DPP4 inhibitors were more commonly used in some regions despite lack of associated benefits on outcomes. Furthermore, evidence-based medications for HF were underused, despite their well-recognized benefit in patients with DM.

Supplementary Information

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

Appendix S1. ASIAN-HF Investigators.

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

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