Effects of combined renin-angiotensin-aldosterone system inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction

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Effects of combined RAAS inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction: Insights from BIOSTAT-CHF and ASIAN-HF registries

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Key Points

Question: Are better outcomes associated with lower combined doses of both ACEi/ARB and β-blockers, versus the high target doses of either β-blockers or ACEi/ARBs alone, and which should have priority during up-titration?

Findings: In our cohort study we found that lower dose of combined therapy was associated with better outcomes than guideline recommended target doses of either monotherapy. Up-titrating β-blockers was associated with a consistent and greater reduction in hazards of all-cause mortality (HR for 100% GRTD: 0.40, 95% CI 0.25-0.63, compared to no treatment) than corresponding ACEi/ARB up-titration (HR: 0.75, 95% CI 0.53-1.07).

Meaning: Achieving lower doses of both β-blocker and ACEi/ARB was associated with better outcome than high dose of monotherapy, where up-titrating β-blockers to target dose resulted in greater mortality reduction.

Abstract

Background. Angiotensin-converting-enzyme inhibitors (ACEi)/Angiotensin receptor blockers (ARB) and β-blockers are guideline-recommended first-line therapies in heart-failure with reduced ejection fraction (HFrEF). Previous studies showed that *individual* drug classes were under-dosed in many parts of Europe and Asia. In this study we investigated the association of *combined* up-titration of ACEi/ARBs and β-blockers on all-cause mortality and its combination with hospitalization for HF.

Methods and Results. 6,787 HFrEF patients (mean age 62.6 ±13.2 years, 77.7% men, mean LVEF 27.7 ±7.2%) were enrolled in prospective multinational European (BIOSTAT-CHF; n=2,100) and Asian (ASIAN-HF; n= 4,687) studies. Outcomes were analysed according to achieved % guideline-recommended target doses (GRTD) of combination ACEi/ARB and β-blocker therapy, adjusted for indication bias.

Results. Only 14% (n=981) patients achieved ≥50% GRTD for both ACEi/ARB and β-blocker. Best outcomes were observed in patients who achieved 100% GRTD of both ACEi/ARB and β-blocker (HR 0.32, 95% CI 0.26-0.39 vs. none). Lower dose of combined therapy was associated with better outcomes than 100% GRTD of either monotherapy. Up-titrating β-blockers was associated with a consistent and greater reduction in hazards of all-cause mortality (HR for 100% GRTD: 0.40, 95% CI 0.25-0.63) than corresponding ACEi/ARB up-titration (HR: 0.75, 95% CI 0.53-1.07).

Conclusion.

This study shows that best outcomes were observed in patients attaining GRTD for both ACEi/ARB and β-blockers, unfortunately this was rarely achieved. Achieving >50% GRTD of both drug classes was associated with better outcome than target dose of monotherapy. Up-titrating β-blockers to target dose was associated with greater mortality reduction than up-titrating ACEi/ARB.

Key words:

Heart failure, reduced ejection fraction, evidence-based pharmacotherapy, outcomes, up-titration

Translational Perspective: Our findings can inform clinical practice, particularly when managing sick patients with multi-morbidity requiring polypharmacy. Best outcomes are obtained with 100% GRTDs, however, under circumstances when it is challenging to up-titrate both ACEi/ARB and β-blockers, achieving moderate doses of both drug classes is more important than reaching maximal target doses of only one class of drug, and further up-titrating β-blockers to 100% GRTD may be associated with greater mortality benefit than up-titrating ACEi/ARB.

Introduction

Current international guidelines[1,2] recommend up-titration of evidence-based medications [angiotensin-converting enzyme-inhibitors (ACEi)/angiotensin II receptor blockers (ARB) and β-blocker] in patients with heart failure and reduced ejection fraction (HFrEF) to target doses used in clinical trials. The recommendations are based on evidence from large randomized clinical trials that both ACEi and β-blockers, up-titrated to respective target doses, improve clinical outcomes in patients with mild to moderate HFrEF[3–13]. Furthermore, studies directly comparing low versus high doses showed (trends towards) superiority of higher doses of ACEi/ARB and β-blocker compared with lower doses[14–16]. However, in daily clinical practice, patients often fail to achieve guideline-recommended target doses (GRTD)[17–21]. Patients with HF frequently have multiple comorbidities and require polypharmacy, making it challenging to successfully up-titrate multiple classes of HF medications[22].

Previous studies showed that *individual* drug classes of ACEi/ARB and β-blocker were under-dosed among patients with HFrEF in many parts of Europe and Asia[20,21]. However, we did not previously examine the effect of *combination* therapies on outcomes. In the current study, we aimed to determine the association of *combined* up-titration of ACEi/ARB and β-blockers with the first occurrence of all-cause mortality or hospitalization for HF and all-cause mortality in patients with HFrEF. Specifically, we aimed to address two key questions in clinical practice:

1. Are better outcomes associated with lower combined doses of both ACEi/ARB and β-blockers, versus the high target doses of either β-blockers or ACEi/ARBs alone?
2. In combination therapy of both β-blockers and ACEi/ARBs, which one (i.e. ACEi/ARB or β-blocker) should have priority during up-titration?

Such practical questions are very unlikely to be answered in further large randomized controlled trials, but yet are clinically very relevant to day-to-day practice. We therefore sought to provide the best available evidence from real world data to guide these clinically important decisions.

Methods

Patient population

The design of BIOSTAT-CHF and ASIAN-HF registry have been published[23–25]. In brief, BIOSTAT-CHF[23] enrolled 2,516 adult patients with HFrEF (left ventricular ejection fraction [LVEF] ≤40%) from 69 participating centres in 11 European countries. The ASIAN-HF registry[24,26] is a multinational registry including 5,276 adult patients with HFrEF (LVEF ≤40%) from 46 investigation sites across 11 regions in Asia. All patients had symptoms and signs of HF and objective evidence of reduced LVEF, and were followed up for clinical outcomes of death and hospitalization. Ethics approvals were obtained from the local institutional review committee of each participating centre and all participating subjects gave informed consent. This study conforms to the ethical guidelines as laid down in the Declaration of Helsinki.

Medication and data collection

HF medications and their target doses were defined according to ESC guidelines[1,27]. Maximum total daily doses attained during follow-up were calculated as a percentage of the guideline-recommended target daily doses (GRTD). Doses were grouped into four categories (0%, 1–49%, 50-99% and ≥100% of GRTD per drug class, resulting in 16 possible treatment group combinations of ACEi/ARB and β-blocker. Patients were considered successfully up-titrated when ≥50% recommended target doses for both ACEi/ARBs and β-blockers were achieved after

up-titration[1,27]. While the use (versus non-use) of mineralocorticoid receptor antagonists (MRA) was considered, no specific MRA up-titration strategy was used in BIOSTAT-CHF or ASIAN-HF. We therefore did not include MRA dosage up-titration in our analyses, but corrected for MRA prescription.

Outcomes

The primary outcome of interest was the composite of all-cause mortality or hospitalization for HF. We also assessed all-cause mortality alone and admission to hospital because of worsening HF as secondary outcomes. Events were adjudicated by an adjudication committee in ASIAN-HF, but in BIOSTAT-CHF, adjudication was done by the treating physicians. However, a systematic meta-analysis failed to detect any effect of event adjudication on study conclusions of cardiovascular outcome trials and the numbers of events included in the final analyses were minimally changed[28].

Statistical analysis

We analysed data from 16 groups of patients achieving combinations of 0%, 1–49%, 50-99% and ≥100% of GRTD of ACEi/ARB and β-blocker. In order to have enough statistical power in all 16 treatment groups, we combined both ASIAN-HF and BIOSTAT-CHF cohorts. We corrected for being included in either ASIAN-HF or BIOSTAT-CHF in all analyses. Results for each group were summarized using standard descriptive statistics including, as appropriate, mean ± standard deviation (SD) and median plus 25th-75th percentiles or numbers and percentages. We tested differences between groups using the Kruskal-Wallis test (for contiguous variables) or the χ^2 test (for categorical variables).

Recognizing that both BIOSTAT-CHF and ASIAN-HF were observational non-randomized studies, we were careful to adjust for treatment indication bias in outcome analysis. We used three methods for adjustment: Propensity score matching, inverse probability weighting with the probability to reach recommended dose and a multivariable analysis with treatment dose as covariate. We only reported results of inverse probability weighting because all methods showed similar results. All analyses for the effects of ACEi/ARB and β-blocker treatment were inversely weighted for the probability of achieving ≥50% GRTD[29,30]. These weights were calculated by the mean probability per patient across all imputation sets, predicted by a penalized logistic model. For the penalized (LASSO) logistic regression analysis predicting successful treatment, we included a comprehensive list of 41 clinical variables (Table S1). Heart rate at baseline was also included in the models correcting for treatment indication bias. To prevent overfit of our statistical models, we used the LASSO regression analyses to select the most parsimonious model[31,32]. All variables were normalized using Box-Cox transformations where necessary[33,34]. Missing values were imputed 5 times using multi-chain Monte Carlo methods Gibbs sampling[35]. We did 10-fold cross validation to ensure optimal penalty parameters and used all analyses for each imputed dataset[36,37].

We used multivariable Cox proportional hazards regression models to examine the association of percentage of GRTD prescribed (0%, 1–49%, 50-99% and ≥100%) by therapeutic class and their interactions with outcome, corrected for the different cohorts. For the HF-hospitalization analysis a competing risk analysis was performed with all-cause mortality as competing risk. Furthermore, to investigate the differences between sex, we undertook stratified Cox proportional hazards models on sex.

A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using R, A Language and Environment for Statistical Computing, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

From a total of 7,792 patients (2,516 from BIOSTAT-CHF and 5,276 from ASIAN-HF), 6,787 patients with LVEF ≤ 40% and information on ACEi/ARB and β-blocker up-titration (2,100 from BIOSTAT-CHF and 4,687 from ASIAN-HF, mean age 62.6 ±13.2 years, 77.7% men, mean LVEF 27.7 ±7.21%) were included in this analysis. Median follow-up of 2,100 patients from BIOSTAT-CHF (22 months [25th-75th percentile 17-27 months] was similar to that in 4,687 patients from ASIAN-HF (21 [11-25] months) (Supplementary Figure S1). Patients from both cohorts were predominantly older men with a history of hypertension and ischaemic aetiology of HF; however patients from ASIAN-HF were on average ~7 years younger with lower body mass index (25 vs 28 kg/m^2), less atrial fibrillation (19 vs 43%) but more diabetes (41 vs 32%) compared to those from BIOSTAT-CHF. Although there was a lower proportion of patients with severe [New York Heart Association (NYHA) class III/IV] symptoms in ASIAN-HF (34 vs 60%), more patients in ASIAN-HF had HF hospitalization within the past year compared to BIOSTAT-CHF (63 vs 32%) (Table S2). All subsequent analyses corrected for cohort.

Baseline characteristics of patients achieving the different treatment dose combinations of guideline-recommended ACEi/ARB and β-blocker target doses are presented in Table 1 (selected dose groups to illustrate characteristics of patients with predominant ACEi/ARB vs β-blocker up-titration) and Table S3 (all 16 groups of dose combinations of the two drug classes). As expected, compared to patients not receiving the drug or receiving only low doses, patients who achieved higher doses were younger, had higher blood pressure and better renal function (for ACEi/ARB up-titration) at baseline, and were more likely to have a history of hypertension or myocardial infarction but less likely to have a history of chronic obstructive pulmonary disease (for β-blocker up-titration). Among the 41 clinical variables included in multivariable models, country of

origin/enrolment, younger age, higher systolic/diastolic blood pressure, hypertension, current smoking and history of myocardial infarction were significant independent predictors which were positively associated with attainment of ≥50% GRTD for either therapeutic class. In contrast, the presence of peripheral oedema, higher NYHA class, chronic obstructive pulmonary disease and increasing serum creatinine levels were negatively associated with attainment of GRTDs (Table S4). This model had an AUC of 0.72 and 0.71 when correcting for optimism.

Of the 6,787 patients, only 14% (n= 981) patients achieved ≥50% GRTD and 3% (n=190) achieved 100% GRTD for both ACEi/ARB and β-blocker (Table 2). The majority (52%) of patients only achieved 1-49% of the GRTD of β-blockers, regardless of ACEi/ARB, with little heterogeneity between BIOSTAT-CHF and ASIAN-HF sub-cohorts (Figure 1).

Association of achieved dose (0%, 1-49%, 50-99% and ≥100%) with all-cause mortality or heart failure-related hospitalization

After adjusting for indication bias and correcting for cohorts, increasing doses towards recommended ACEi/ARB and β-blocker doses were generally associated with a decreasing risk of a composite outcome (mortality or heart failure hospitalization), Figure 2a. When any dose (up to 49% GRTD) was given for both ACEi/ARB and β-blocker, the hazard of composite outcome was lower (Hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.61-0.84) compared with none (Table 2). Increasing the doses further to 50-99% GRTD for either ACEi/ARB or β-blocker in combination therapy reduced the hazards markedly (HR 0.50/0.61). Of note, the reduction in hazards observed for these combinations, even though not reaching 100% GRTD in either drug class, was greater than that observed with the attainment of 100% GRTD for ACEi/ARB alone (HR 0.71, 95% CI 0.52-0.96) or 100% GRTD for β-blocker alone (HR 0.68, 95% CI 0.49-

0.93)(Table 2). Treating patients at sub-optimal ACE/ARB and BB doses (1-49% of GDMT) appears not to be better than treating patients at high dose of either single therapy. However, as soon as one of the treatment doses is increased to at least 50% of guideline dose, the risks reduce to 0.61 (95% CI 0.49-0.75) and 0.50 (95% CI 0.42-0.61) which is lower than 0.67 and 0.71 for the groups with <50% GDMT. Achievement of 100% of recommended doses for ACEi/ARB and β-blockers was associated with the lowest hazard ratios (HR 0.32 CI 0.26-0.39). Correcting for MRA prescription did not alter the risks of the separate treatment groups. Sex modified the association of medication doses with composite outcomes (p=0.001). In stratified analyses, for all outcomes, women benefited more at lower doses than men, even with sub-optimal doses of <50% GRTD (supplementary table S5).

Association of achieved dose (0%, 1-49%, 50-99% and ≥100%) with all-cause mortality

Compared to patients not treated with ACEi/ARB and β-blockers, the lowest risk in all-cause mortality was observed in those achieving 100% GRTD for both therapeutic classes (with HR 0.19, 95% CI 0.14-0.24, Table 2, Figure 2b). The second lowest risk HR 0.27 (95% CI 0.21-0.34) was among those with 50-99% target dose for ACEi/ARB and 100% target dose for β-blockers. As monotherapy, achievement of 100% GRTD for ACEi/ARB was not associated with additional mortality benefit compared to lower doses of ACEi/ARB; in contrast, increasing doses of β-blockers as monotherapy was associated with steady reduction in hazards for mortality (from HR 0.75 [95% CI 0.6-0.92] with 1-49% GRTD, to 0.65 [95% CI, 0.48-0.87] with 50-99% GRTD, to 0.4 [95% CI 0.25-0.63] with 100% GRTD).

Association of achieved dose (0%, 1-49%, 50-99% and ≥100%) with HF-related hospitalization

Increasing doses of combinations of ACE-inhibitors/ARBs and β-blockers were not directly associated with risk of HF-hospitalization (Table 2, Figure 2c), although a lower risk was seen in patients with increasing dose of single therapy of ACE-inhibitors/ARBs.

Discussion

Our key findings from our multinational observational studies are: In both Europe and Asia, achievement of full GRTD for both ACEi/ARB and β-blockers was rare. Not surprisingly, the best outcomes were observed in those who achieved 100% GRTD of combined therapy. However, in the vast majority of patients not reaching 100% GRTD, taking any dose combination was better than none, and achieving lower doses of both drug classes was associated with better outcomes than reaching the highest dose of only one class. For mortality reduction, up-titrating β-blockers to 100% GRTD was associated with greater benefit than up-titrating ACEi/ARB to 100% GRTD. The key practical questions we sought to answer in this study are very unlikely to be answered in large randomized controlled trials, yet very relevant to day-to-day clinical practice. In RCTs, novel drugs are given on top of standard of care. However, regarding standard of care, the main outcome papers of these RCTs only provide data on whether ACEi/ARB/BB/MRA etc are used or not (yes/no) but the doses as percentage of the guideline-recommended target doses are never reported. In this paper these data are provided which makes them even more important.

There are few previous reports on the doses of first-line evidence-based pharmacotherapy in HFrEF patients [20,21,38–40]. Despite robust evidence showing the benefits of attainment of GRTD of ACEi/ARB[14,16] and β-blockers [15,41,42] , many studies report failure to achieve guideline-target

doses in usual care setting[20,21,38,39,43,44], and even in the trial setting, with CIBIS-II[10], CIBIS-ELD[45] and HF-ACTION[46] showing that ≤25% to ≤50%, of patients achieve target doses of β-blockers[42]. Reasons for failure to achieve guideline-targeted doses are multifactorial and include patients' clinical status, drug intolerance or adverse effects (for instance hypotension, bradycardia, renal impairment, hyperkalaemia, and other real or perceived side effects), physicians' prescribing patterns, polypharmacy and lack of compliance, as well as cost constraints[47]. Our results are consistent with contemporary US-based data, with the recently reported CHAMP-HF (Change the Management of Patients with Heart Failure) registry[38,39] showing that <20% of eligible patients were receiving target doses of ACEi/ARBs and β-blockers, even among those with systolic blood pressure ≥110 mm Hg, and a remarkably low 1% of patients receiving target doses of ACEi/ARBs, β-blockers and MRAs. The CHAMP-HF registry also systematically analysed reasons for lack of up-titration of medications and found that among those who were treated with ACEi/ARBs, higher systolic blood pressure and a history of hypertension (for ACEi/ARBs), black race, and obesity/diabetes (for β-blockers) were associated with achieving target doses; whereas prior HF hospitalization within 12 months, asthma/ chronic obstructive pulmonary disease, and NYHA functional class III/IV status were associated with sub-target doses. For all-cause mortality, graduated decreases in relative risk of deaths with increasing doses of ACEi/ARBs and beta-blockers were observed (Figure 2b). In contrast, the association of high doses of medications observed in HFH (Figure 2c), could potentially stem from other non-medical factors, e.g. limited access to care; differences in health care systems across geography, particularly in regard to coordinated primary care following discharge; variation in delivery and quality of cardiac care, and others as reported in the QUALIFY international registry[48–50].

In light of the known challenges in day-to-day practice of achieving 100% target doses of combination therapies in HFrEF, our results emphasize that "some is better than none". These results add to that of studies in the SOLVD and CIBIS II trials, which showed the effects of low dose enalapril[51] or bisoprolol[52] as single therapy. The TRED-HF trial[53] showed that withdrawal of treatment studied the effect of evidence-based medical treatment withdrawal. All studies show that patients already benefit from small doses of guideline-directed medical therapies. Thus, initiating and maintaining guideline-directed medical therapies in patients with HFrEF remains a quintessential aim in the management of these patients, even when target dose is not reached.

However, how do we manage dose titration in cases where full target doses of combination drugs cannot be achieved (for instance when blood pressure is borderline)? Our results suggest that up-titration to even sub-target doses of both ACEi/ARBs and β-blockers was associated with better outcomes than full up-titration to 100% target doses of a single drug class (with either none or very low doses of the other drug class). This is not to say that attempts at up-titration are not important in real world practice; on the contrary we showed that achievement of higher doses of both guideline-recommended drug classes was associated with reduction in composite outcomes of death and HF hospitalization, consistent with prior trial evidence comparing lower versus higher doses of guideline-directed medical therapies. In the ATLAS trial[14], treatment with high (32.5 to 35mg) vs low (2.5 to 5mg) daily doses lisinopril was associated with a non-significant 8% lower hazard of death but a significant 12% lower risk of all-cause death or hospitalization, and 24% fewer hospitalizations for HF. Similar findings were found in the HEAAL trial, with the use of low dose (50mg) vs. high dose (150mg) losartan[16]. In both trials, symptomatic hypotension/syncope and renal insufficiency, and hyperkalaemia (only in HEAAL trial), were

more prevalent in the high dose group. The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial[54] was undertaken to establish the efficacy and safety of two doses (low-5mg/day; high-20mg/day) of long-term carvedilol vs. placebo, in Japanese patients with HF and LVEF ≤40%. There was no statistical difference in outcomes between the high and low dose of carvediolol. High (≥25 mg/day) vs. low dose (<25 mg/day) carvedilol equivalents in HF-ACTION also conferred similar benefit for all-cause mortality and CV outcomes, although high dose was superior (albeit with marginal significance) for a composite outcome of all-cause mortality or HF hospitalization[38,39]. Our results build on these prior trials and suggest that when faced with the clinical conundrum of up-titrating both drugs versus up-titrating only one of the drugs to maximal target doses, the former may be a preferable approach. Furthermore, we observed that up-titrating β-blockers to 100% GRTD was associated with mortality benefit, even when doses of ACEi/ARB were still sub-target. As a cautionary note, the guidelines advised slow uptitration of β-blockers due to a possible transient HF worsening during the first 2 weeks after upstart with β-blockers.

This contemporary prospective multinational study spans a huge geography in Europe and Asia. Both studies were designed with a specific investigator-directed question regarding reasons for not achieving recommended doses; however, in a large proportion of cases there was a lack of further specification of the reason for not achieving GRTD other than 'unknown'. Specific contraindications to further uptitration of medications were not captured, although those with absolute contraindications to ACEi/ARBs at baseline remained small. The impact of incident renal failure on discontinuation of treatment could not been examined.

Robust statistical analytical methods were used and we corrected for indication bias; unfortunately, if this correction was sufficient is untestable and there remains potential for residual bias. We further acknowledge that lack of persistence and adherence to medications may play a role, but cannot be directly measured in our study. We were unable to assess the change in heart rate with up-titration of β-blockers. While concurrent use of MRAs were accounted for (vs non-use), we did not assess different doses of MRAs. Nonetheless, our observation 'real world' data from large cohorts may provide the best available evidence to guide clinically important decisions which are unlikely to be tested in future large randomized controlled trials.

Conclusions

Our multinational real-world data suggest that although best outcomes were observed in patients attaining 100% GRTD for both ACEi/ARB and β-blockers, such combined maximal up-titration was rarely achieved. Achieving lower doses of both drug classes to at least 50% GRTD was associated with better outcomes than reaching the target dose of only one class; and further up-titrating β-blockers to 100% GRTD was associated with greater mortality benefit than up-titrating ACEi/ARB. Our data suggest that less is better than nothing, but since this is not a randomized controlled trial, no strong recommendations can be made. The only recommendation that can be made is that ACEi/ARB and beta-blockers should be uptitrated to the recommended doses as stated in all heart failure guidelines.

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Declaration of interests (alphabetical order):

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APPENDIX I

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Figure legends

Figure 1: Distribution of ACEi/ARB and β-blocker in ASIAN-HF and BIOSTAT-CHF

Figure 2 A: Hazard Ratio of mortality and/or HF-related hospitalization for patients achieving a combination of 0, 1-49, 50-99% and ≥100% recommended treatment dose of ACEi/ARB and β-blocker dose; **B:** Hazard Ratio of mortality for patients achieving a combination of 0, 1-49, 50-99% and ≥100% recommended treatment dose of ACEi/ARB and β-blocker dose; **C:** Hazard Ratio of HF-related hospitalization for patients achieving a combination of 0, 1-49, 50-99% and ≥100% recommended treatment dose of ACEi/ARB and β-blocker dose;

Table 1: Baseline characteristics of patients achieving low dose, high dose and target dose of guideline recommended treatment

Variable	All	A0B0	A0B1	A0B2	A0B3	P for trend B1 to B3 (A0)	A1B0	A2B0	A3B0	P for trend A1 to A3 (B0)	Other
n	6787	502	782	245	133		380	234	135	-	4376
n (ASIAN-HF)	4687 (69.1%)	482 (96%)	656 (83.9%)	203 (82.9%)	115 (86.5%)	<0.0001	320 (84.2%)	189 (80.8%)	118 (87.4%)	<0.0001	2604 (59.5%)
Sex (Male)	5271 (77.7%)	376 (74.9%)	615 (78.6%)	192 (78.4%)	101 (75.9%)	0.43	290 (76.3%)	174 (74.4%)	98 (72.6%)	0.84	3425 (78.3%)
Age (years)	62.6 (13.16)	63.9 (13.13)	63.9 (13.49)	61.3 (14.37)	60.4 (13.85)	0.001	63.4 (13.85)	62.4 (12.82)	59.7 (14.23)	0.002	62.3 (12.9)
Former smoker	2504 (36.9%)	146 (29.1%)	265 (33.9%)	101 (41.2%)	53 (39.8%)	0.001	131 (34.5%)	78 (33.3%)	32 (23.7%)	0.14	1698 (38.8%)
Current smoker	913 (13.5%)	44 (8.8%)	103 (13.2%)	21 (8.6%)	17 (12.8%)		42 (11.1%)	23 (9.8%)	13 (9.6%)		650 (14.9%)
Chronic obstructive pulmonary disease	726 (10.7%)	68 (13.7%)	81 (10.4%)	27 (11%)	12 (9%)	0.25	52 (13.7%)	39 (16.7%)	18 (13.3%)	0.69	429 (9.8%)
Myocardial infarction	2211 (48.1%)	151 (53.9%)	275 (54.3%)	82 (56.6%)	50 (59.5%)	0.79	123 (53%)	69 (52.3%)	40 (59.7%)	0.77	1421 (45.1%)
Ischaemic aetiology	3343 (51.4%)	226 (50.1%)	417 (56.3%)	115 (50%)	69 (56.1%)	0.12	199 (55.6%)	115 (50.7%)	60 (48.4%)	0.35	2142 (50.5%)
NYHA Class III/IV	2691 (42.7%)	193 (50%)	352 (50.1%)	106 (45.7%)	50 (41%)	0.2	158 (45.9%)	89 (40.6%)	45 (35.7%)	0.018	1698 (40.8%)
Peripheral oedema	2058 (30.4%)	122 (24.6%)	216 (27.6%)	68 (27.8%)	37 (27.8%)	0.64	128 (33.7%)	73 (31.2%)	44 (32.6%)	0.02	1370 (31.3%)
Orthopnea	1664 (24.5%)	140 (28.1%)	210 (26.9%)	56 (22.9%)	37 (27.8%)	0.49	102 (26.8%)	58 (24.8%)	36 (26.7%)	0.83	1025 (23.4%)
Pulmonary rales	951 (16.7%)	76 (15.5%)	116 (15.9%)	35 (15.2%)	20 (15.9%)	1	79 (21.9%)	50 (23.9%)	31 (25%)	0.013	544 (15.9%)
Previous HF-hospitalization in past year	2247 (48.8%)	184 (66.4%)	327 (60.2%)	99 (57.6%)	57 (60.6%)	0.22	131 (60.4%)	64 (47.8%)	42 (47.7%)	<0.0001	1343 (43.5%)
Atrial Fibrillation	1765 (26%)	102 (20.5%)	197 (25.2%)	80 (32.7%)	33 (24.8%)	0.004	87 (22.9%)	38 (16.2%)	15 (11.1%)	0.013	1213 (27.7%)
Diabetes mellitus	2607 (38.4%)	199 (40%)	339 (43.4%)	94 (38.4%)	67 (50.4%)	0.09	149 (39.2%)	90 (38.5%)	59 (43.7%)	0.78	1610 (36.8%)
Hypertension	3708 (54.7%)	273 (54.8%)	429 (54.9%)	145 (59.2%)	80 (60.2%)	0.45	163 (42.9%)	99 (42.3%)	63 (46.7%)	0.001	2456 (56.2%)
Body mass index (kg/m^2)	25.9 (5.4)	24.3 (4.73)	24.6 (4.96)	25.8 (5.33)	25.2 (4.97)	0.001	24.5 (4.92)	25.5 (5.11)	26.5 (7.45)	<0.0001	26.4 (5.44)
Heart rate (beats/min)	79.6 (17.26)	82.8 (18.17)	78.5 (16.72)	78.3 (16.01)	80 (17.28)	0.004	82 (18.46)	82.1 (18.48)	81.9 (18.69)	0.55	79.1 (17.03)
Systolic blood pressure (mmHg)	120 (20.58)	118.1 (21.1)	116.4 (18.45)	120.9 (21.3)	121.4 (21.38)	0.028	115.4 (19.46)	119.3 (19)	119.6 (20.66)	0.33	121.1 (20.86)
Diastolic blood pressure (mmHg)	73.1 (12.74)	72.5 (12.72)	70.5 (11.7)	73.3 (12.15)	73.8 (13.44)	0.21	70.2 (12.01)	72.5 (11.77)	73.8 (12.6)	0.41	73.8 (12.96)
LVEF (%)	27.7 (7.21)	28.2 (7.02)	27.9 (7.14)	28 (6.93)	28.5 (6.9)	0.97	27.4 (7.04)	28.2 (6.61)	28.3 (6.55)	0.94	27.5 (7.33)

NT-proBNP (ng/L)	3641 (1720-8103)	5410 (2178-11721)	5300 (2009-16530)	4295 (1806-10279)	4663.8 (1947-11059)	0.64	3278 (1987-6980)	3282 (1567-7729)	1997.5 (1235-4910)	0.035	3366 (1631-7086)
eGFR (ml/min/1.73m^2)	68.2 (28.64)	58.2 (28.88)	59.7 (30.59)	60.5 (29.39)	59.4 (30.15)	0.44	66.6 (28.68)	72 (27.77)	71.3 (23.83)	<0.0001	71.3 (27.63)

A0=ACEi/ARB 0%;A1=ACEi/ARB 1-49%;
A2=ACEi/ARB-50-99%;
A3=ACEi/ARB≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB-50-99%; B3=BB≥100%

p=statistical differences between the subgroups

Table 2: Hazard ratio (95% confidence interval) of patients achieving specific target dose for Mortality or HF-hospitalization, Mortality and HF-hospitalization

	Mortality or HF-hospitalization			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	1.00 (reference)	0.98 (0.83-1.17; 0.85)	0.90 (0.71-1.15; 0.41)	0.68 (0.49-0.93; 0.02)
1-49% ACEi/ARB	0.90 (0.73-1.10; 0.30)	0.71 (0.61-0.84; <0.001)	0.61 (0.49-0.75; <0.001	0.80 (0.62-1.04; 0.10)
50-99% ACEi/ARB	0.67 (0.52-0.87; 0.002)	0.50 (0.42-0.61; <0.001)	0.64 (0.54-0.75; <0.001)	0.57 (0.48-0.68; <0.001)
100% ACEi/ARB	0.71 (0.52-0.96; 0.03)	0.52 (0.42-0.64; <0.001)	0.66 (0.56-0.77; <0.001)	0.32 (0.26-0.39; <0.001)
	Mortality			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	1.00 (reference)	0.75 (0.60-0.92; 0.006)	0.65 (0.48-0.87; 0.004)	0.40 (0.25-0.63; <0.001)
1-49% ACEi/ARB	0.74 (0.57-0.95; 0.02)	0.57 (0.47-0.69; <0.001)	0.39 (0.29-0.51; <0.001)	0.58 (0.42-0.81; 0.001)
50-99% ACEi/ARB	0.57 (0.42-0.78; <0.001)	0.33 (0.26-0.42; <0.001)	0.42 (0.34-0.51; <0.001)	0.27 (0.21-0.34; <0.001)
100% ACEi/ARB	0.75 (0.53-1.07; 0.11)	0.40 (0.30-0.52; <0.001)	0.38 (0.31-0.46; <0.001)	0.19 (0.14-0.24; <0.001)
	HF-hospitalization			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	1.00 (reference)	1.42 (1.14-1.77; 0.002)	1.48 (1.12-1.95; 0.006)	1.10 (0.76-1.59; 0.62)
1-49% ACEi/ARB	1.26 (0.97-1.63;0.08)	1.08 (0.88-1.33; 0.43)	0.94 (0.72-1.21; 0.64)	1.14 (0.83-1.57; 0.41)
50-99% ACEi/ARB	0.80 (0.57-1.11; 0.18)	0.75 (0.59-0.95; 0.02)	0.93 (0.76-1.14; 0.50)	1.14 (0.92-1.41; 0.22)
100% ACEi/ARB	0.71 (0.46-1.09; 0.12)	0.81 (0.62-1.05; 0.12)	1.14 (0.93-1.40; 0.20)	0.85 (0.68-1.06; 0.17)

Table S1: Variables used in inverse probability weighting

Variable	Summary	Percentage missing
n	6787	11 %
ASIAN-HF	4687 (69.1%)	0 %
East Asia	1544 (22.7%)	0 %
South Asia	1314 (19.4%)	
South-East Asia	1829 (26.9%)	
North EU	950 (14%)	
South EU	1150 (16.9%)	
Country (China)	440 (6.5%)	0 %
Country (Hong Kong)	50 (0.7%)	
Country (India)	1314 (19.4%)	
Country (Indonesia)	158 (2.3%)	
Country (Japan)	527 (7.8%)	
Country (Korea)	272 (4%)	
Country (Malaysia)	490 (7.2%)	
Country (Philippines)	24 (0.4%)	
Country (Singapore)	1030 (15.2%)	
Country (Taiwan)	255 (3.8%)	
Country (Thailand)	127 (1.9%)	
Country (Netherlands)	276 (4.1%)	
Country (Germany)	84 (1.2%)	
Country (France)	195 (2.9%)	
Country (Greece)	278 (4.1%)	
Country (Italy)	289 (4.3%)	
Country (Norway)	93 (1.4%)	
Country (Poland)	244 (3.6%)	
Country (Serbia)	366 (5.4%)	
Country (Slovenia)	22 (0.3%)	
Country (Sweden)	96 (1.4%)	
Country (UK)	157 (2.3%)	
Age (years)	62.6 (13.16)	0 %
Sex (Male)	5271 (77.7%)	0 %
Race (Caucasian)	2078 (30.6%)	0 %
Race (Chinese)	1475 (21.7%)	
Race (Indians)	1505 (22.2%)	
Race (Malay)	651 (9.6%)	
Race (Japanese)	528 (7.8%)	
Race (Korean)	272 (4%)	
Race (Thai)	127 (1.9%)	
Race (Filipino)	9 (0.1%)	
Race (Indigenous SEA)	106 (1.6%)	
Race (Other)	33 (0.5%)	
NYHA class 1	633 (10.1%)	7 %
NYHA class 2	2972 (47.2%)	
NYHA class 3	2199 (34.9%)	
NYHA class 4	492 (7.8%)	
Orthopnea present	1664 (24.5%)	0 %
Height (m)	166.4 (9.54)	3 %
Weight (kg)	72.2 (18.11)	3 %
BMI (kg/m^2)	25.9 (5.4)	3 %
Heart rate (beats/min)	79.6 (17.26)	1 %
Systolic blood pressure (mmHg)	120 (20.58)	0 %
Diastolic blood pressure (mmHg)	73.1 (12.74)	0 %
jugular venous pressure	1132 (18.6%)	10 %
Peripheral oedema	2058 (30.4%)	0 %
Rales	951 (16.7%)	16 %
Hepatomegaly	542 (8%)	0 %
Ischemic aetiology	3343 (51.4%)	4 %
Previous hospitalization for heart failure	2247 (48.8%)	32 %
Device therapy (ICD only)	368 (5.4%)	0 %
Device therapy (Pacemaker only)	260 (3.8%)	
Device therapy (Biventricular Pacer only)	124 (1.8%)	
Device therapy (Biventricular Pacer and ICD)	464 (6.9%)	
Coronary artery disease	3336 (49.2%)	0 %
Myocardial infarction	2211 (48.1%)	32 %
Percutaneous coronary intervention	1390 (30.3%)	32 %
Valvular surgery	717 (15.6%)	32 %
Atrial Fibrillation	1765 (26%)	0 %

Hypertension	3708 (54.7%)	0 %
Stroke	502 (7.4%)	0 %
Peripheral artery disease	378 (5.6%)	0 %
Chronic obstructive pulmonary disease	726 (10.7%)	0 %
Diabetes mellitus	2607 (38.4%)	0 %
Smoking (Ever)	2504 (36.9%)	0 %
Smoking (Never)	913 (13.5%)	
Alcohol history	1139 (16.8%)	0 %
Serum Creatinine (μmol/L)	4.7 (0.44)	14 %
Estimated GFR, calculated with MDRD	68.2 (28.64)	15 %
Sodium (mmol/L)	138.6 (4.03)	20 %
Potassium (mmol/L)	4.3 (0.56)	17 %
Haemoglobin (g/dL)	13.2 (2.01)	20 %
Blood Urea Nitroge n(mmol/L)	10.3 (8.78)	33 %
log-NT-proBNP (ng/L)	8.2 (7.45-9)	68 %
log-BNP (ng/L)	6.3 (5.23-7.28)	85 %
LVEF (%)	28 (22-34)	3 %

Table S2: Baseline characteristics for ASIAN-HF and BIOSTAT-CHF cohorts

Variable	ASIAN.HF	BIOSTAT-CHF	p value	excluded ASIAN-HF	excluded BIOSTAT-CHF
n	4687	2100		589	416
Sex (Male)	3682 (78.6%)	1589 (75.7%)	0.008	441 (74.9%)	257 (61.8%)
Age (years)	60.3 (13.03)	67.7 (11.95)	<0.0001	58.7 (13.19)	75 (9.97)
Ischaemic aetiology	2189 (49.8%)	1154 (55%)	0.0001	281 (51.5%)	204 (49%)
NYHA Class III/IV	1455 (34.3%)	1236 (60.3%)	<0.0001	213 (39.6%)	286 (72.2%)
peripheral oedema	1070 (22.9%)	988 (47%)	<0.0001	171 (30.1%)	268 (64.4%)
Orthopnea	986 (21.1%)	678 (32.3%)	<0.0001	200 (35.1%)	201 (48.6%)
pulmonary rales	768 (16.4%)	183 (18%)	0.22	111 (19.5%)	65 (23.8%)
Previous HF-hospitalization in past year	1578 (62.9%)	669 (31.9%)	<0.0001	193 (65%)	125 (30%)
Atrial Fibrillation	864 (18.5%)	901 (42.9%)	<0.0001	77 (13.6%)	242 (58.2%)
Diabetes mellitus	1931 (41.2%)	676 (32.2%)	<0.0001	189 (33.3%)	143 (34.4%)
Hypertension	2431 (51.9%)	1277 (60.8%)	<0.0001	288 (50.8%)	292 (70.2%)
Body mass index (kg/m^2)	24.9 (5.06)	28 (5.52)	<0.0001	24.6 (5.51)	27.4 (5.34)
Heart rate (beats/min)	79.5 (16.19)	79.8 (19.43)	0.51	80.9 (15.84)	80.8 (19.71)
Systolic blood pressure (mmHg)	118.1 (19.99)	124.2 (21.24)	<0.0001	121.1 (20.03)	127.3 (24.85)
Diastolic blood pressure (mmHg)	72 (12.45)	75.5 (13.05)	<0.0001	75.2 (13.19)	71.9 (14.52)
LVEF (%)	27.3 (7.06)	28.6 (7.49)	<0.0001	28.1 (22-34)	45 (35-55)
NT-proBNP (ng/L)	3294 (1436-8103)	4024 (2253-8185)	<0.0001	4023 (1339-11849)	4495 (2713-9000)
eGFR (ml/min/1.73m^2)	66.1 (27.85)	71.9 (29.65)	<0.0001	63 (27.11)	64.2 (28.79)
Combined Endpoint	1441 (31%)	741 (35%)			
All-cause mortality	864 (18%)	423 (20%)			
Heart failure hospitalization	1119 (24%)	500 (24%)			

Table S3: Baseline characteristics of groups achieving 0%, 1-49%, 50-99% and 100% guideline recommended target doses for ACE-inhibitor/ARB and beta-blocker

Variable	All	A0B0	A0B1	A0B2	A0B3	A1B0	A1B1	A1B2	A1B3
n	6787	502	782	245	133	380	1524	458	185
n (ASIAN-HF)	4687 (69.1%)	482 (96%)	656 (83.9%)	203 (82.9%)	115 (86.5%)	320 (84.2%)	1049 (68.8%)	305 (66.6%)	134 (72.4%)
Sex (Male)	5271 (77.7%)	376 (74.9%)	615 (78.6%)	192 (78.4%)	101 (75.9%)	290 (76.3%)	1188 (78%)	366 (79.9%)	151 (81.6%)
Age (years)	62.6 (13.16)	63.9 (13.13)	63.9 (13.49)	61.3 (14.37)	60.4 (13.85)	63.4 (13.85)	62.1 (12.95)	62.3 (12.59)	61.5 (12.49)
Former smoker	2504 (36.9%)	146 (29.1%)	265 (33.9%)	101 (41.2%)	53 (39.8%)	131 (34.5%)	567 (37.2%)	156 (34.1%)	86 (46.5%)
Current smoker	913 (13.5%)	44 (8.8%)	103 (13.2%)	21 (8.6%)	17 (12.8%)	42 (11.1%)	257 (16.9%)	71 (15.5%)	23 (12.4%)
Chronic obstructive pulmonary disease	726 (10.7%)	68 (13.7%)	81 (10.4%)	27 (11%)	12 (9%)	52 (13.7%)	154 (10.1%)	47 (10.3%)	13 (7%)
Myocardial infarction	2211 (48.1%)	151 (53.9%)	275 (54.3%)	82 (56.6%)	50 (59.5%)	123 (53%)	492 (46.9%)	139 (45.3%)	61 (47.3%)
Ischaemic aetiology	3343 (51.4%)	226 (50.1%)	417 (56.3%)	115 (50%)	69 (56.1%)	199 (55.6%)	740 (50.4%)	219 (49.5%)	93 (52.8%)
NYHA Class III/IV	2691 (42.7%)	193 (50%)	352 (50.1%)	106 (45.7%)	50 (41%)	158 (45.9%)	571 (40.2%)	157 (36%)	53 (29.8%)
Peripheral oedema	2058 (30.4%)	122 (24.6%)	216 (27.6%)	68 (27.8%)	37 (27.8%)	128 (33.7%)	463 (30.4%)	135 (29.5%)	58 (31.4%)
Orthopnea	1664 (24.5%)	140 (28.1%)	210 (26.9%)	56 (22.9%)	37 (27.8%)	102 (26.8%)	348 (22.9%)	101 (22.1%)	42 (22.7%)
Pulmonary rales	951 (16.7%)	76 (15.5%)	116 (15.9%)	35 (15.2%)	20 (15.9%)	79 (21.9%)	222 (17.1%)	51 (13.5%)	17 (11%)
Previous HF-hospitalization in past year	2247 (48.8%)	184 (66.4%)	327 (60.2%)	99 (57.6%)	57 (60.6%)	131 (60.4%)	470 (49%)	141 (45.2%)	73 (55.3%)
Atrial Fibrillation	1765 (26%)	102 (20.5%)	197 (25.2%)	80 (32.7%)	33 (24.8%)	87 (22.9%)	403 (26.5%)	148 (32.3%)	74 (40%)
Diabetes mellitus	2607 (38.4%)	199 (40%)	339 (43.4%)	94 (38.4%)	67 (50.4%)	149 (39.2%)	539 (35.4%)	177 (38.6%)	82 (44.3%)
Hypertension	3708 (54.7%)	273 (54.8%)	429 (54.9%)	145 (59.2%)	80 (60.2%)	163 (42.9%)	740 (48.6%)	239 (52.2%)	112 (60.5%)
Body mass index (kg/m^2)	25.9 (5.4)	24.3 (4.73)	24.6 (4.96)	25.8 (5.33)	25.2 (4.97)	24.5 (4.92)	25.3 (5.02)	25.9 (4.91)	26.4 (5.34)
Heart rate (beats/min)	79.6 (17.26)	82.8 (18.17)	78.5 (16.72)	78.3 (16.01)	80 (17.28)	82 (18.46)	78.5 (16.51)	78.8 (15.9)	80.9 (18.27)
Systolic blood pressure (mmHg)	120 (20.58)	118.1 (21.1)	116.4 (18.45)	120.9 (21.3)	121.4 (21.38)	115.4 (19.46)	115.8 (18.71)	118.3 (20.28)	119.8 (19.2)
Diastolic blood pressure (mmHg)	73.1 (12.74)	72.5 (12.72)	70.5 (11.7)	73.3 (12.15)	73.8 (13.44)	70.2 (12.01)	70.5 (11.95)	72.6 (12.78)	71.7 (12.83)
LVEF (%)	27.7 (7.21)	28.2 (7.02)	27.9 (7.14)	28 (6.93)	28.5 (6.9)	27.4 (7.04)	26.6 (7.37)	27.2 (7.36)	27.6 (7.25)
NT-proBNP (ng/L)	3641 (1720-8103)	5410 (2178-11721)	5300 (2008-16530)	4295 (1806-10279)	4664 (1947-11059)	3278 (1987-6980)	3236 (1480-7114)	3009 (1598-7083)	3510 (2271-7616)
eGFR (ml/min/1.73m^2)	68.2 (28.64)	58.2 (28.88)	59.7 (30.59)	60.5 (29.39)	59.4 (30.15)	66.6 (28.68)	70.8 (27.43)	69.4 (28.78)	62.9 (27.16)
Potassium (mmol/L)	6787	4.2 (0.64)	4.3 (0.55)	4.3 (0.56)	4.3 (0.57)	4.2 (0.53)	4.2 (0.54)	4.3 (0.57)	4.2 (0.52)
MRA use at baseline		173 (34%)	410 (52%)	146 (60%)	77 (58%)	214 (56%)	952 (62%)	280 (61%)	109 (59%)

A0=ACEi/ARB 0%;A1=ACEi/ARB 1-49%; A2=ACEi/ARB-50-99%; A3=ACEi/ARB≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB-50-99%; B3=BB≥100%

Variable	A2B0	A2B1	A2B2	A2B3	A3B0	A3B1	A3B2	A3B3	p
n	234	797	340	178	135	431	273	190	
n (ASIAN-HF)	189 (80.8%)	428 (53.7%)	160 (47.1%)	109 (61.2%)	118 (87.4%)	201 (46.6%)	120 (44%)	98 (51.6%)	<0.0001
Sex (Male)	174 (74.4%)	619 (77.7%)	268 (78.8%)	135 (75.8%)	98 (72.6%)	334 (77.5%)	219 (80.2%)	145 (76.3%)	0.7
Age (years)	62.4 (12.82)	63.1 (12.73)	61.9 (13.09)	59.7 (14.27)	59.7 (14.23)	64.6 (12.47)	62.2 (12.26)	59.9 (13.71)	<0.0001
Former smoker	78 (33.3%)	292 (36.6%)	155 (45.6%)	80 (44.9%)	32 (23.7%)	170 (39.4%)	112 (41%)	80 (42.1%)	<0.0001
Current smoker	23 (9.8%)	110 (13.8%)	50 (14.7%)	22 (12.4%)	13 (9.6%)	53 (12.3%)	40 (14.7%)	24 (12.6%)	
Chronic obstructive pulmonary disease	39 (16.7%)	84 (10.5%)	31 (9.1%)	14 (7.9%)	18 (13.3%)	41 (9.5%)	28 (10.3%)	17 (8.9%)	0.047
Myocardial infarction	69 (52.3%)	264 (44.7%)	123 (45.4%)	58 (49.2%)	40 (59.7%)	143 (42.1%)	89 (42.2%)	52 (38%)	0.0001
Ischaemic aetiology	115 (50.7%)	395 (50.3%)	185 (55.7%)	88 (51.5%)	60 (48.4%)	217 (51.3%)	129 (48.9%)	76 (41.3%)	0.07
NYHA Class III/IV	89 (40.6%)	340 (44.4%)	134 (41.2%)	65 (38%)	45 (35.7%)	191 (45.6%)	117 (44.2%)	70 (37.6%)	<0.0001
Peripheral oedema	73 (31.2%)	242 (30.4%)	117 (34.4%)	48 (27%)	44 (32.6%)	152 (35.3%)	96 (35.2%)	59 (31.1%)	0.039
Orthopnea	58 (24.8%)	205 (25.7%)	77 (22.6%)	39 (21.9%)	36 (26.7%)	114 (26.5%)	61 (22.3%)	38 (20%)	0.27
Pulmonary rales	50 (23.9%)	104 (17.5%)	35 (15.2%)	18 (12.7%)	31 (25%)	56 (17.8%)	28 (15.2%)	13 (9.8%)	0.002
Previous HF-hospitalization in past year	64 (47.8%)	244 (40.8%)	104 (40.8%)	60 (44.8%)	42 (47.7%)	104 (32.2%)	83 (37.6%)	64 (42.7%)	<0.0001
Atrial Fibrillation	38 (16.2%)	180 (22.6%)	93 (27.4%)	57 (32%)	15 (11.1%)	111 (25.8%)	88 (32.2%)	59 (31.1%)	<0.0001
Diabetes mellitus	90 (38.5%)	282 (35.4%)	118 (34.7%)	75 (42.1%)	59 (43.7%)	167 (38.7%)	95 (34.8%)	75 (39.5%)	0.003
Hypertension	99 (42.3%)	464 (58.3%)	203 (59.7%)	112 (62.9%)	63 (46.7%)	289 (67.1%)	176 (64.5%)	121 (63.7%)	<0.0001
Body mass index (kg/m^2)	25.5 (5.11)	26.4 (5.01)	27.6 (6.18)	27.9 (5.19)	26.5 (7.45)	27.3 (5.89)	28.4 (6.02)	28.4 (6.15)	<0.0001
Heart rate (beats/min)	82.1 (18.48)	78.7 (16.63)	79.6 (17.23)	81.9 (19)	81.9 (18.69)	78.7 (17.13)	79.2 (17.92)	81.8 (19.77)	<0.0001
Systolic blood pressure (mmHg)	119.3 (19)	122.1 (20.15)	125.9 (20.65)	123.3 (19.4)	119.6 (20.66)	128.8 (23.46)	127.7 (21.89)	130.5 (23.5)	<0.0001
Diastolic blood pressure (mmHg)	72.5 (11.77)	74.6 (12.45)	76.3 (12.32)	76.3 (12.25)	73.8 (12.6)	77.5 (13.19)	79.2 (14.68)	79.5 (13.76)	<0.0001
LVEF (%)	28.2 (6.61)	27.8 (7.17)	27.7 (7.25)	28.3 (7.37)	28.3 (6.55)	29.1 (7.13)	28 (7.48)	28.3 (7.22)	<0.0001
NT-proBNP (ng/L)	3282 (1567-7729)	3596 (1852-7378)	3048 (1547-6907)	4241 (2399-8523)	1998 (1235-4910)	3274 (2008-6441)	3457 (1936-6121)	2496 (1200-5145)	<0.0001
eGFR (ml/min/1.73m^2)	72 (27.77)	72.2 (25.86)	73.3 (26.06)	69.7 (28.3)	71.3 (23.83)	74 (29.45)	71.9 (28.5)	75.6 (28.64)	<0.0001
Potassium (mmol/L)	4.2 (0.58)	4.3 (0.56)	4.3 (0.53)	4.2 (0.55)	4.3 (0.62)	4.3 (0.59)	4.3 (0.53)	4.3 (0.49)	0.4695
MRA use	124 (53%)	481 (60%)	185 (54%)	97 (54%)	78 (58%)	249 (58%)	160 (59%)	109 (57%)	<0.001

A0=ACEi/ARB 0%;A1=ACEi/ARB 1-49%; A2=ACEi/ARB-50-99%; A3=ACEi/ARB≥100%

B0=BB 0%; B1=BB 1-49%; B2=BB-50-99%; B3=BB≥100%

Table S4: Results of multivariate logistic analyses predicting attainment of ≥50% GRTD for either ACEi/ARB or β-blockers

Variable	OR	95% CI	p-value
(Intercept)	0.00	(0-30.45)	0.11
Country (China)	-	-	-
Country (Hong Kong)	12.48	(3.88-40.10)	<0.0001
Country (India)	6.78	(3.07-14.96)	<0.0001
Country (Indonesia)	11.80	(4.73-29.46)	<0.0001
Country (Japan)	3.15	(1.29-7.69)	0.01
Country (Korea)	25.78	(11.39-58.35)	<0.0001
Country (Malaysia)	14.21	(6.33-31.94)	<0.0001
Country (Philippines)	6.58	(1.26-34.41)	0.03
Country (Singapore)	7.94	(3.57-17.65)	<0.0001
Country (Taiwan)	3.94	(1.55-9.99)	0.004
Country (Thailand)	9.10	(3.51-23.61)	<0.0001
Country (Netherlands)	32.56	(14.20-74.63)	<0.0001
Country (Germany)	25.64	(10.08-65.22)	<0.0001
Country (France)	39.42	(17.09-90.89)	<0.0001
Country (Greece)	3.23	(1.27-8.22)	0.01
Country (Italy)	15.82	(6.81-36.78)	<0.0001
Country (Norway)	37.68	(15.33-92.61)	<0.0001
Country (Poland)	17.24	(7.44-39.96)	<0.0001
Country (Serbia)	12.72	(5.62-28.78)	<0.0001
Country (Slovenia)	31.65	(9.70-103.22)	<0.0001
Country (Sweden)	71.73	(29.56-174.05)	<0.0001
Country (UK)	8.82	(3.46-22.50)	<0.0001
Age (years)	0.98	(0.97-0.99)	<0.0001
Sex (male)	1.06	(0.83-1.35)	0.63
LVEF (%)	1.00	(0.99-1.01)	0.65
HF-hospitalization in year before inclusion	0.87	(0.71-1.06)	0.16
Orthopnea present	0.83	(0.67-1.03)	0.1
Height (m)	1.01	(0.98-1.04)	0.52
Weight (kg)	1.01	(0.98-1.04)	0.56
Body mass index (kg/m2)	1.02	(0.94-1.11)	0.64

Rales	0.91	(0.72-1.16)	0.46
Ischemic aetiology	0.90	(0.74-1.08)	0.26
Percutaneous coronary intervention	1.14	(0.95-1.38)	0.17
Alcohol usage	1.02	(0.83-1.25)	0.84
NYHA class I	-	-	-
NYHA class II	0.83	(0.64-1.08)	0.16
NYHA class III	0.83	(0.62-1.11)	0.2
NYHA class IV	0.58	(0.37-0.91)	0.02
Myocardial infarction	1.21	(1.00-1.47)	0.048
Heart Rate (bpm)	1.00	(0.99-1.00)	0.27
Systolic blood pressure (mmHg)	1.01	(1.00-1.01)	<0.0001
Diastolic blood pressure (mmHg)	1.01	(1.00-1.02)	0.013
Peripheral oedema present	0.82	(0.69-0.99)	0.037
Atrial Fibrillation	1.09	(0.91-1.31)	0.33
Hypertension	1.31	(1.11-1.55)	0.0017
Peripheral Artery Disease	0.76	(0.54-1.07)	0.11
Chronic obstructive pulmonary disease	0.76	(0.58-0.98)	0.03
Smoking (never)	-	-	-
Smoking (current)	1.20	(1.00-1.43)	0.0495
Smokin (ever)	1.00	(0.78-1.28)	0.99
log-B-type natriuretic peptide (ng/L)	0.99	(0.93-1.04)	0.59
Hemoglobin (g/dL)	1.02	(0.97-1.06)	0.46
eGFR (ml/min/1.73m2)	0.99	(0.99-1.00)	0.056
serum Creatinine μmol/L	0.49	(0.29-0.83)	0.008
Sodium (mmol/L)	1.01	(0.99-1.04)	0.31
Potassium (mmol/L)	1.16	(1.01-1.34)	0.04
Blood Urea Nitrogen (mmol/L)	1.00	(0.98-1.01)	0.71
log-N-terminal-pro-BNP (ng/L)	0.96	(0.89-1.03)	0.23

Table S5: Hazard ratio (95% confidence interval) of patients achieving specific target dose for Mortality or HF-hospitalization, Mortality and HF-hospitalization stratified by sex.

MEN	Mortality or HF-hospitalization			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	0.94 (0.77-1.15; 0.55)	0.87 (0.67-1.14; 0.32)	0.60 (0.41-0.88; 0.01)
1-49% ACEi/ARB	0.89 (0.71-1.13; 0.35)	0.74 (0.62-0.89; 0.001)	0.62 (0.49-0.79; <0.001)	0.78 (0.58-1.04; 0.09)
50-99% ACEi/ARB	0.62 (0.46-0.83; 0.002)	0.51 (0.41-0.63; <0.001)	0.70 (0.59-0.84; <0.001)	0.56 (0.46-0.69; <0.001)
100% ACEi/ARB	0.60 (0.41-0.88; 0.008)	0.50 (0.39-0.64; <0.001)	0.63 (0.52-0.75; <0.001)	0.31 (0.25-0.39; <0.001)
	Mortality			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	0.73 (0.57-0.93; 0.01)	0.64 (0.45-0.91; 0.01)	0.37 (0.21-0.63; <0.001)
1-49% ACEi/ARB	0.75 (0.56-1.00; 0.05)	0.64 (0.51-0.80; <0.001)	0.40 (0.30-0.55; <0.001)	0.63 (0.43-0.91; 0.01)
50-99% ACEi/ARB	0.56 (0.39-0.81; 0.002)	0.35 (0.27-0.46; <0.001)	0.49 (0.40-0.61; <0.001)	0.29 (0.22-0.38; <0.001)
100% ACEi/ARB	0.74 (0.49-1.13; 0.16)	0.42 (0.31-0.57; <0.001)	0.39 (0.31-0.50; <0.001)	0.15 (0.11-0.21; <0.001)
	HF-hospitalization			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	1.44 (1.11-1.87; 0.006)	1.59 (1.14-2.21; 0.006)	1.16 (0.74-1.82; 0.51)
1-49% ACEi/ARB	1.39 (1.03-1.88; 0.03)	1.18 (0.92-1.50; 0.19)	1.02 (0.76-1.39; 0.88)	1.22 (0.84-1.78; 0.30)
50-99% ACEi/ARB	0.82 (0.55-1.23; 0.33)	0.85 (0.64-1.12; 0.25)	0.91 (0.65-1.27; 0.57)	1.11 (0.75-1.65; 0.61)
100% ACEi/ARB	0.68 (0.4-1.16; 0.15)	0.88 (0.64-1.21; 0.41)	1.05 (0.74-1.48; 0.80)	0.81 (0.53-1.24; 0.33)
WOMEN	**Mortality or HF-hospitalization**			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	1.11 (0.77-1.61; 0.58)	1.00 (0.61-1.65; 0.99)	0.94 (0.51-1.74; 0.84)
1-49% ACEi/ARB	0.88 (0.56-1.38; 0.59)	0.59 (0.41-0.84; 0.003)	0.51 (0.31-0.84; 0.008)	0.86 (0.47-1.55; 0.61)
50-99% ACEi/ARB	0.85 (0.51-1.42; 0.54)	0.47 (0.31-0.71; <0.001)	0.43 (0.30-0.61; <0.001)	0.56 (0.39-0.82; 0.003)
100% ACEi/ARB	1.06 (0.61-1.86; 0.83)	0.58 (0.37-0.91; 0.02)	0.77 (0.55-1.09; 0.1416)	0.35 (0.24-0.53; <0.001)
	Mortality			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	0.79 (0.52-1.20; 0.27)	0.67 (0.37-1.22; 0.194	0.47 (0.21-1.06; 0.07)
1-49% ACEi/ARB	0.71 (0.43-1.19; 0.19)	0.34 (0.23-0.52; <0.001)	0.33 (0.18-0.60; <0.001)	0.44 (0.20-0.96; 0.04)
50-99% ACEi/ARB	0.58 (0.32-1.05; 0.07)	0.28 (0.17-0.45; <0.001)	0.21 (0.14-0.32; <0.001)	0.22 (0.14-0.36; <0.001)
100% ACEi/ARB	0.74 (0.49-1.13; 0.16)	0.42 (0.31-0.57; <0.001)	0.39 (0.31-0.50; <0.001)	0.15 (0.11-0.21; <0.001)
	HF-hospitalization			
	0% BB	**1-49% BB**	**50-99% BB**	**100% BB**
0% ACEi/ARB	-	1.68 (1.00-2.82; 0.05)	1.88 (0.98-3.60; 0.057)	1.62 (0.72-3.65; 0.25)
1-49% ACEi/ARB	1.18 (0.62-2.23; 0.62)	1.34 (0.83-2.18; 0.23)	1.40 (0.76-2.59; 0.2791)	1.51 (0.67-3.40; 0.32)
50-99% ACEi/ARB	1.26 (0.62-2.56; 0.53)	0.99 (0.57-1.72; 0.97)	0.88 (0.43-1.83; 0.7355)	1.63 (0.79-3.39; 0.19)
100% ACEi/ARB	1.10 (0.47-2.58; 0.83)	1.34 (0.74-2.44; 0.34)	1.59 (0.81-3.13; 0.1795)	0.75 (0.30-1.86; 0.53)

Figure 1

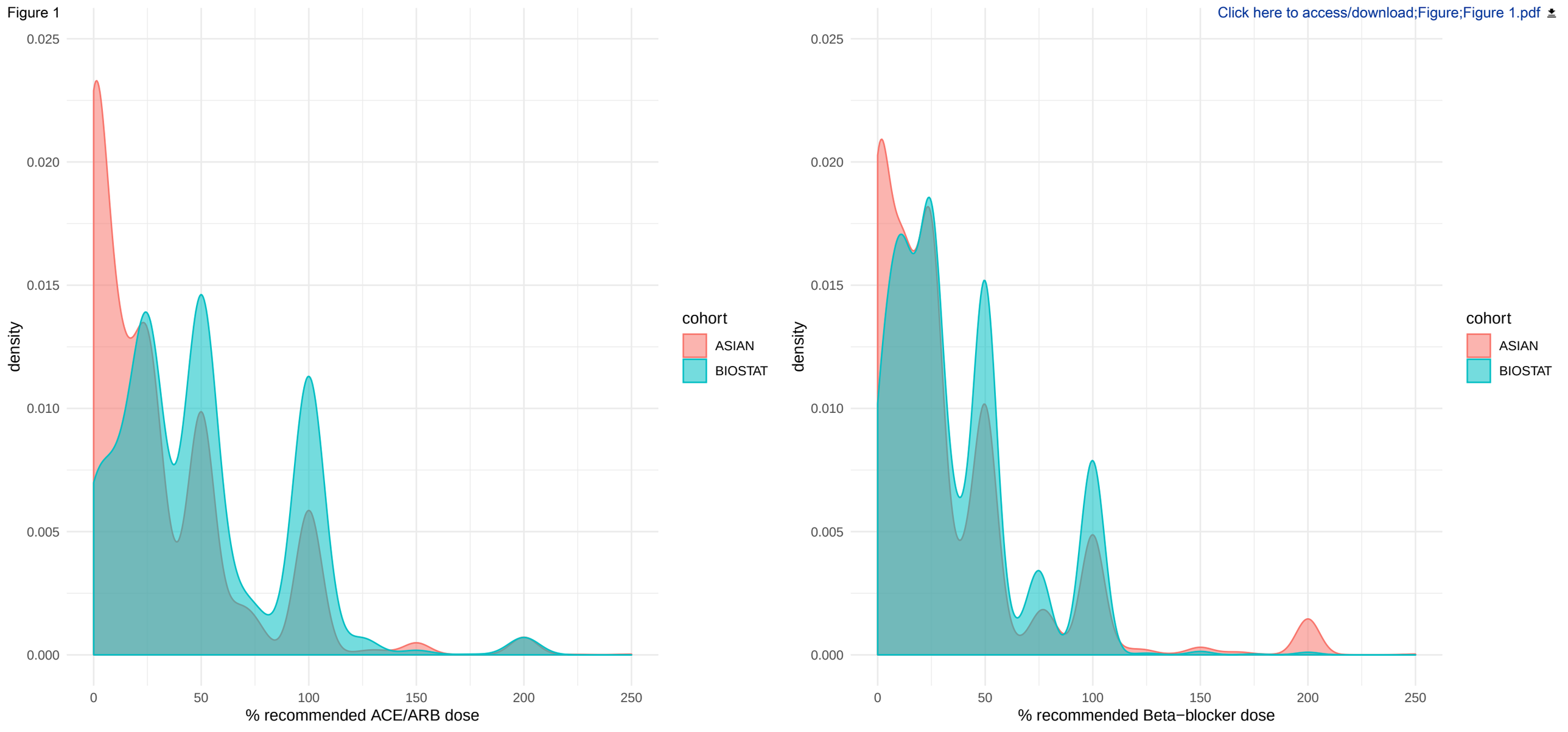

Figure 2a

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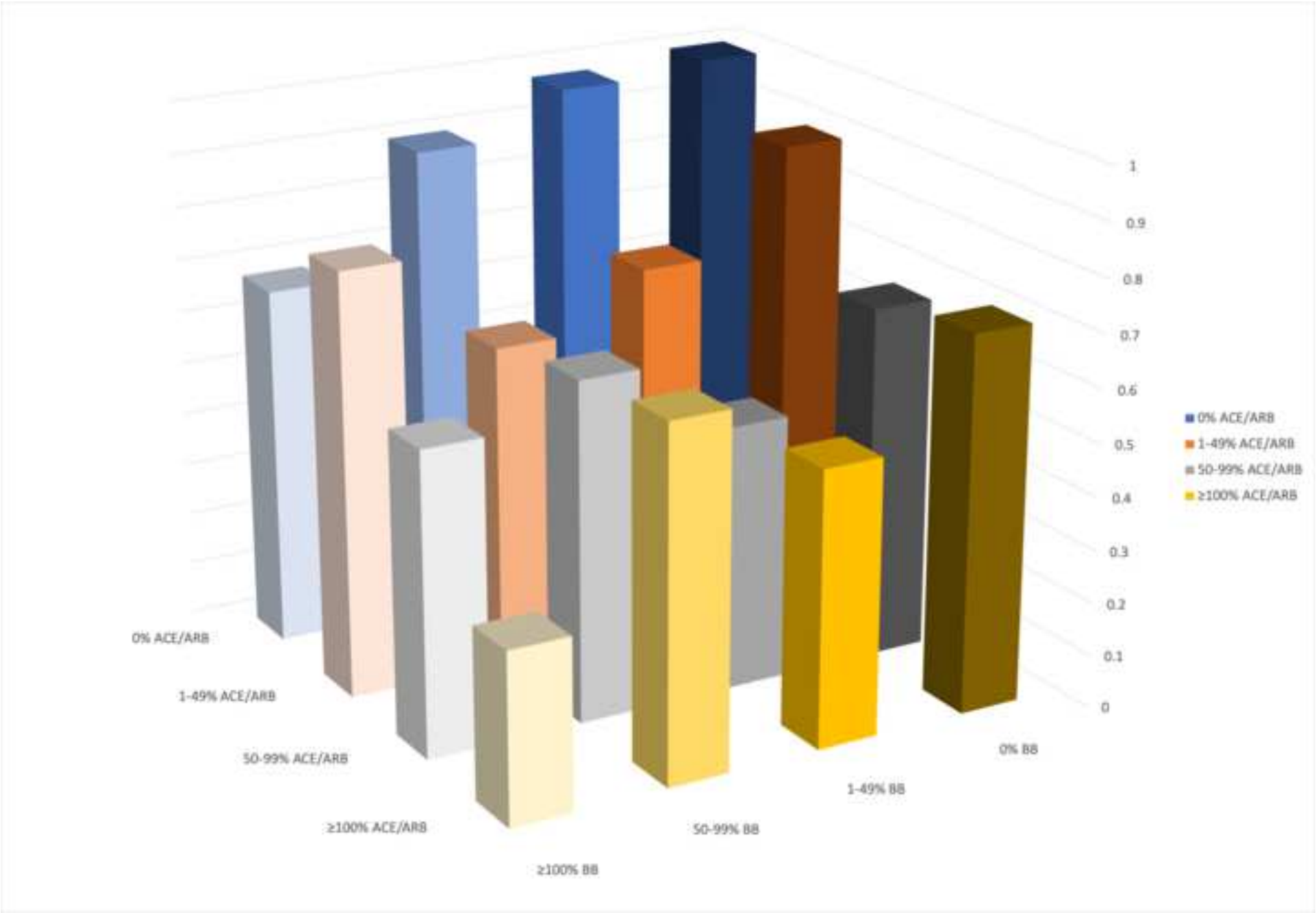

Figure 2b

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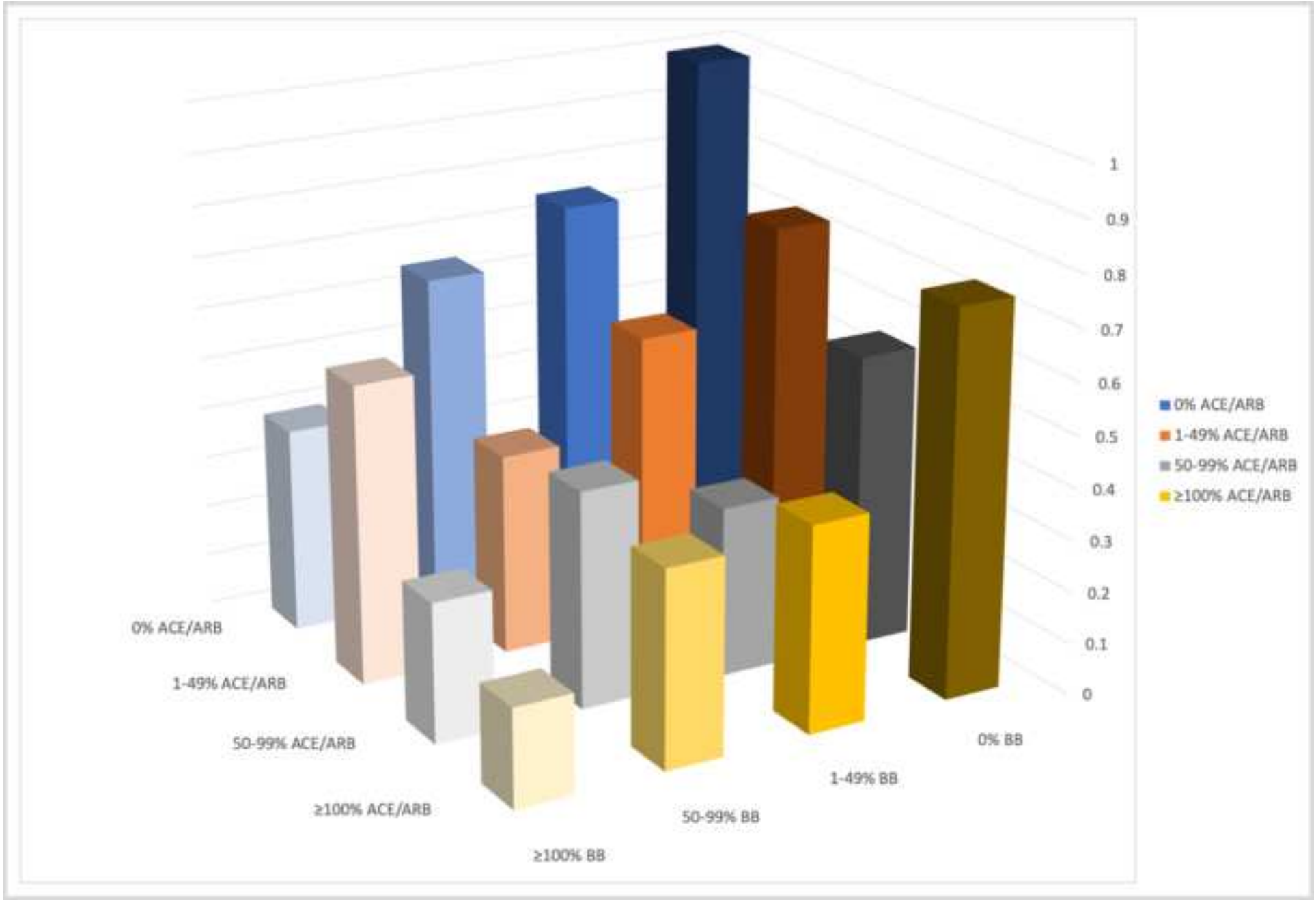

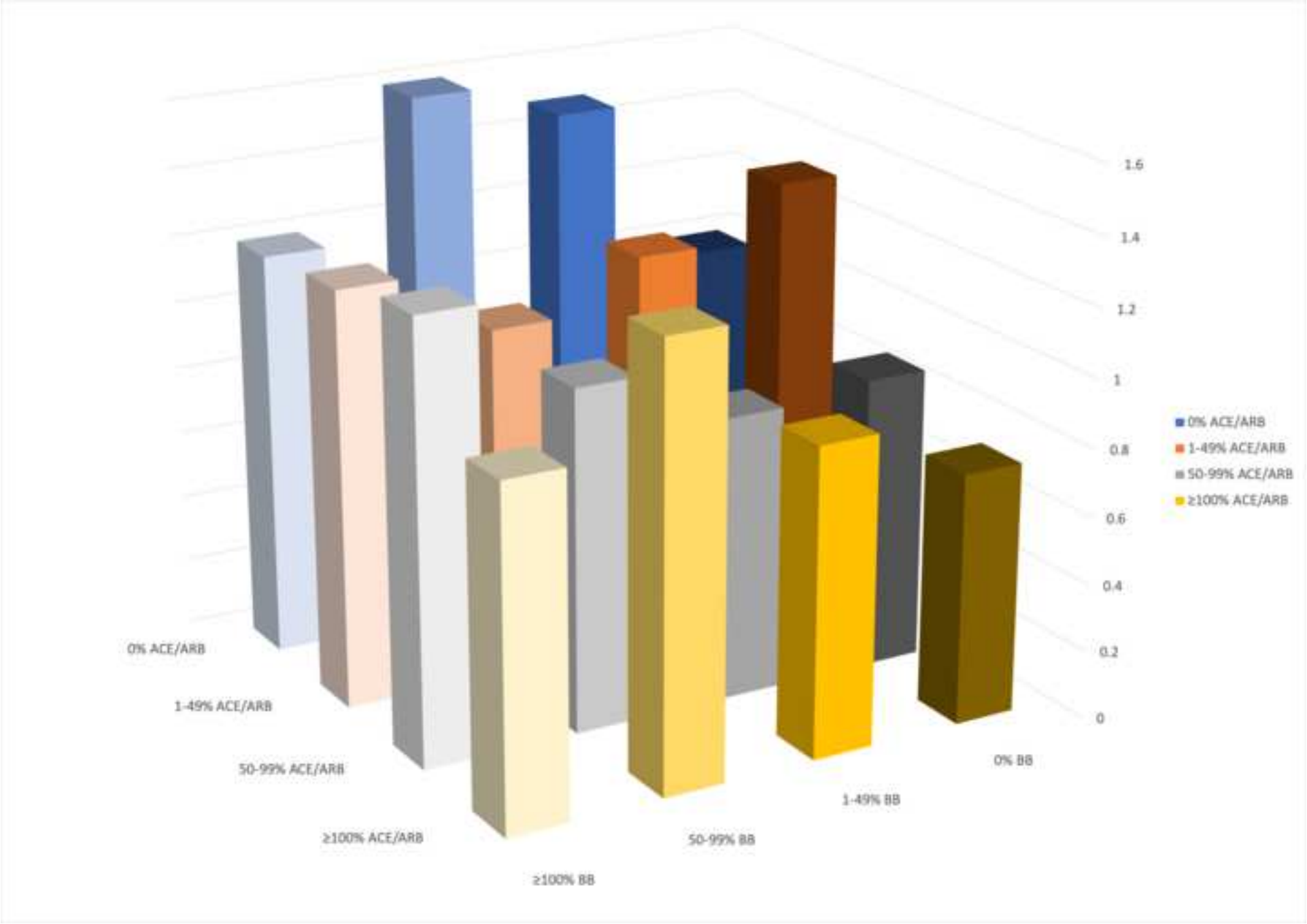

Figure S1 Flow chart

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