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

4

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1 **Key Points**

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

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

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

13

1 **Abstract**

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

8

9 **Methods and Results.** 6,787 HFrEF patients (mean age 62.6 ± 13.2 years, 77.7% men, mean
10 LVEF $27.7 \pm 7.2\%$) were enrolled in prospective multinational European (BIOSTAT-CHF;
11 $n=2,100$) and Asian (ASIAN-HF; $n= 4,687$) studies. Outcomes were analysed according to
12 achieved % guideline-recommended target doses (GRTD) of combination ACEi/ARB and β -
13 blocker therapy, adjusted for indication bias.

14

15 **Results.** Only 14% ($n=981$) patients achieved $\geq 50\%$ GRTD for both ACEi/ARB and β -blocker.
16 Best outcomes were observed in patients who achieved 100% GRTD of both ACEi/ARB and β -
17 blocker (HR 0.32, 95% CI 0.26-0.39 vs. none). Lower dose of combined therapy was associated
18 with better outcomes than 100% GRTD of either monotherapy. Up-titrating β -blockers was
19 associated with a consistent and greater reduction in hazards of all-cause mortality (HR for 100%
20 GRTD: 0.40, 95% CI 0.25-0.63) than corresponding ACEi/ARB up-titration (HR: 0.75, 95% CI
21 0.53-1.07).

22

23

1 **Conclusion.**

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

7

8

9 **Key words:**

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

11

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

1 **Introduction**

2 Current international guidelines^{1,2} recommend up-titration of evidence-based medications
3 [angiotensin-converting enzyme-inhibitors (ACEi)/angiotensin II receptor blockers (ARB) and β -
4 blocker] in patients with heart failure and reduced ejection fraction (HFrEF) to target doses used
5 in clinical trials. The recommendations are based on evidence from large randomized clinical
6 trials that both ACEi and β -blockers, up-titrated to respective target doses, improve clinical
7 outcomes in patients with mild to moderate HFrEF³⁻¹³. Furthermore, studies directly comparing
8 low versus high doses showed (trends towards) superiority of higher doses of ACEi/ARB and β -
9 blocker compared with lower doses¹⁴⁻¹⁶. However, in daily clinical practice, patients often fail to
10 achieve guideline-recommended target doses (GRTD)¹⁷⁻²¹. Patients with HF frequently have
11 multiple comorbidities and require polypharmacy, making it challenging to successfully up-titrate
12 multiple classes of HF medications²².

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

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

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

4

5 **Methods**

6 **Patient population**

7 The design of BIOSSTAT-CHF and ASIAN-HF registry have been published²³⁻²⁵. In brief,
8 BIOSSTAT-CHF²³ enrolled 2,516 adult patients with HFrEF (left ventricular ejection fraction
9 [LVEF] $\leq 40\%$) from 69 participating centres in 11 European countries. The ASIAN-HF
10 registry^{24,26} is a multinational registry including 5,276 adult patients with HFrEF (LVEF $\leq 40\%$)
11 from 46 investigation sites across 11 regions in Asia. All patients had symptoms and signs of HF
12 and objective evidence of reduced LVEF, and were followed up for clinical outcomes of death
13 and hospitalization. Ethics approvals were obtained from the local institutional review committee
14 of each participating centre and all participating subjects gave informed consent. This study
15 conforms to the ethical guidelines as laid down in the Declaration of Helsinki.

16

17 **Medication and data collection**

18 HF medications and their target doses were defined according to ESC guidelines^{1,27}. Maximum
19 total daily doses attained during follow-up were calculated as a percentage of the guideline-
20 recommended target daily doses (GRTD). Doses were grouped into four categories (0%, 1–49%,
21 50-99% and $\geq 100\%$ of GRTD per drug class, resulting in 16 possible treatment group
22 combinations of ACEi/ARB and β -blocker. Patients were considered successfully up-titrated
23 when $\geq 50\%$ recommended target doses for both ACEi/ARBs and β -blockers were achieved after

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

5

6 **Outcomes**

7 The primary outcome of interest was the composite of all-cause mortality or hospitalization for
8 HF. We also assessed all-cause mortality alone and admission to hospital because of worsening
9 HF as secondary outcomes. Events were adjudicated by an adjudication committee in ASIAN-
10 HF, but in BIOSTAT-CHF, adjudication was done by the treating physicians. However, a
11 systematic meta-analysis failed to detect any effect of event adjudication on study conclusions of
12 cardiovascular outcome trials and the numbers of events included in the final analyses were
13 minimally changed²⁸.

14

15 **Statistical analysis**

16 We analysed data from 16 groups of patients achieving combinations of 0%, 1–49%, 50–99% and
17 $\geq 100\%$ of GRTD of ACEi/ARB and β -blocker. In order to have enough statistical power in all 16
18 treatment groups, we combined both ASIAN-HF and BIOSTAT-CHF cohorts. We corrected for
19 being included in either ASIAN-HF or BIOSTAT-CHF in all analyses. Results for each group
20 were summarized using standard descriptive statistics including, as appropriate, mean \pm standard
21 deviation (SD) and median plus 25th–75th percentiles or numbers and percentages. We tested
22 differences between groups using the Kruskal-Wallis test (for contiguous variables) or the χ^2 test
23 (for categorical variables).

1 Recognizing that both BIOSTAT-CHF and ASIAN-HF were observational non-randomized
2 studies, we were careful to adjust for treatment indication bias in outcome analysis. We used
3 three methods for adjustment: Propensity score matching, inverse probability weighting with the
4 probability to reach recommended dose and a multivariable analysis with treatment dose as
5 covariate. We only reported results of inverse probability weighting because all methods showed
6 similar results. All analyses for the effects of ACEi/ARB and β -blocker treatment were inversely
7 weighted for the probability of achieving $\geq 50\%$ GRTD^{29,30}. These weights were calculated by the
8 mean probability per patient across all imputation sets, predicted by a penalized logistic model.
9 For the penalized (LASSO) logistic regression analysis predicting successful treatment, we
10 included a comprehensive list of 41 clinical variables (Table S1). Heart rate at baseline was also
11 included in the models correcting for treatment indication bias. To prevent overfit of our
12 statistical models, we used the LASSO regression analyses to select the most parsimonious
13 model^{31,32}. All variables were normalized using Box-Cox transformations where necessary^{33,34}.
14 Missing values were imputed 5 times using multi-chain Monte Carlo methods Gibbs sampling³⁵.
15 We did 10-fold cross validation to ensure optimal penalty parameters and used all analyses for
16 each imputed dataset^{36,37}.
17 We used multivariable Cox proportional hazards regression models to examine the association of
18 percentage of GRTD prescribed (0%, 1–49%, 50–99% and $\geq 100\%$) by therapeutic class and their
19 interactions with outcome, corrected for the different cohorts. For the HF-hospitalization analysis
20 a competing risk analysis was performed with all-cause mortality as competing risk. Furthermore,
21 to investigate the differences between sex, we undertook stratified Cox proportional hazards
22 models on sex.

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

1 **Results**

2 From a total of 7,792 patients (2,516 from BIOSTAT-CHF and 5,276 from ASIAN-HF), 6,787
3 patients with LVEF $\leq 40\%$ and information on ACEi/ARB and β -blocker up-titration (2,100 from
4 BIOSTAT-CHF and 4,687 from ASIAN-HF, mean age 62.6 ± 13.2 years, 77.7% men, mean
5 LVEF $27.7 \pm 7.21\%$) were included in this analysis. Median follow-up of 2,100 patients from
6 BIOSTAT-CHF (22 months [25th-75th percentile 17-27 months]) was similar to that in 4,687
7 patients from ASIAN-HF (21 [11-25] months) (Supplementary Figure S1). Patients from both
8 cohorts were predominantly older men with a history of hypertension and ischaemic aetiology of
9 HF; however patients from ASIAN-HF were on average ~ 7 years younger with lower body mass
10 index (25 vs 28 kg/m²), less atrial fibrillation (19 vs 43%) but more diabetes (41 vs 32%)
11 compared to those from BIOSTAT-CHF. Although there was a lower proportion of patients with
12 severe [New York Heart Association (NYHA) class III/IV] symptoms in ASIAN-HF (34 vs
13 60%), more patients in ASIAN-HF had HF hospitalization within the past year compared to
14 BIOSTAT-CHF (63 vs 32%) (Table S2). All subsequent analyses corrected for cohort.

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

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

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

11

12 *Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with all-cause mortality or heart*
13 *failure-related hospitalization*

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

1 0.93)(Table 2). Treating patients at sub-optimal ACE/ARB and BB doses (1-49% of GDMT)
2 appears not to be better than treating patients at high dose of either single therapy. However, as
3 soon as one of the treatment doses is increased to at least 50% of guideline dose, the risks reduce
4 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
5 the groups with <50% GDMT. Achievement of 100% of recommended doses for ACEi/ARB and
6 β -blockers was associated with the lowest hazard ratios (HR 0.32 CI 0.26-0.39). Correcting for
7 MRA prescription did not alter the risks of the separate treatment groups. Sex modified the
8 association of medication doses with composite outcomes (p=0.001). In stratified analyses, for all
9 outcomes, women benefited more at lower doses than men, even with sub-optimal doses of <50%
10 GRTD (supplementary table S5).

11

12 *Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with all-cause mortality*

13 Compared to patients not treated with ACEi/ARB and β -blockers, the lowest risk in all-cause
14 mortality was observed in those achieving 100% GRTD for both therapeutic classes (with HR
15 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)
16 was among those with 50-99% target dose for ACEi/ARB and 100% target dose for β -blockers.
17 As monotherapy, achievement of 100% GRTD for ACEi/ARB was not associated with additional
18 mortality benefit compared to lower doses of ACEi/ARB; in contrast, increasing doses of β -
19 blockers as monotherapy was associated with steady reduction in hazards for mortality (from HR
20 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
21 0.4 [95% CI 0.25-0.63] with 100% GRTD).

22

1 *Association of achieved dose (0%, 1-49%, 50-99% and $\geq 100\%$) with HF-related hospitalization*
2 Increasing doses of combinations of ACE-inhibitors/ARBs and β -blockers were not directly
3 associated with risk of HF-hospitalization (Table 2, Figure 2c), although a lower risk was seen in
4 patients with increasing dose of single therapy of ACE-inhibitors/ARBs.

5

6 **Discussion**

7 Our key findings from our multinational observational studies are: In both Europe and Asia,
8 achievement of full GRTD for both ACEi/ARB and β -blockers was rare. Not surprisingly, the
9 best outcomes were observed in those who achieved 100% GRTD of combined therapy.
10 However, in the vast majority of patients not reaching 100% GRTD, taking any dose combination
11 was better than none, and achieving lower doses of both drug classes was associated with better
12 outcomes than reaching the highest dose of only one class. For mortality reduction, up-titrating β -
13 blockers to 100% GRTD was associated with greater benefit than up-titrating ACEi/ARB to
14 100% GRTD. The key practical questions we sought to answer in this study are very unlikely to
15 be answered in large randomized controlled trials, yet very relevant to day-to-day clinical
16 practice. In RCTs, novel drugs are given on top of standard of care. However, regarding standard
17 of care, the main outcome papers of these RCTs only provide data on whether
18 ACEi/ARB/BB/MRA etc are used or not (yes/no) but the doses as percentage of the guideline-
19 recommended target doses are never reported. In this paper these data are provided which makes
20 them even more important.
21 There are few previous reports on the doses of first-line evidence-based pharmacotherapy in
22 HFrEF patients^{20,21,38-40}. Despite robust evidence showing the benefits of attainment of GRTD of
23 ACEi/ARB^{14,16} and β -blockers^{15,41,42}, many studies report failure to achieve guideline-target

1 doses in usual care setting^{20,21,38,39,43,44}, and even in the trial setting, with CIBIS-II¹⁰, CIBIS-
2 ELD⁴⁵ and HF-ACTION⁴⁶ showing that $\leq 25\%$ to $\leq 50\%$, of patients achieve target doses of β -
3 blockers⁴². Reasons for failure to achieve guideline-targeted doses are multifactorial and include
4 patients' clinical status, drug intolerance or adverse effects (for instance hypotension,
5 bradycardia, renal impairment, hyperkalaemia, and other real or perceived side effects),
6 physicians' prescribing patterns, polypharmacy and lack of compliance, as well as cost
7 constraints⁴⁷. Our results are consistent with contemporary US-based data, with the recently
8 reported CHAMP-HF (Change the Management of Patients with Heart Failure) registry^{38,39}
9 showing that $< 20\%$ of eligible patients were receiving target doses of ACEi/ARBs and β -
10 blockers, even among those with systolic blood pressure ≥ 110 mm Hg, and a remarkably low 1%
11 of patients receiving target doses of ACEi/ARBs, β -blockers and MRAs. The CHAMP-HF
12 registry also systematically analysed reasons for lack of up-titration of medications and found
13 that among those who were treated with ACEi/ARBs, higher systolic blood pressure and a history
14 of hypertension (for ACEi/ARBs), black race, and obesity/diabetes (for β -blockers) were
15 associated with achieving target doses; whereas prior HF hospitalization within 12 months,
16 asthma/ chronic obstructive pulmonary disease, and NYHA functional class III/IV status were
17 associated with sub-target doses. For all-cause mortality, graduated decreases in relative risk of
18 deaths with increasing doses of ACEi/ARBs and beta-blockers were observed (Figure 2b). In
19 contrast, the association of high doses of medications observed in HFH (Figure 2c), could
20 potentially stem from other non-medical factors, e.g. limited access to care; differences in health
21 care systems across geography, particularly in regard to coordinated primary care following
22 discharge; variation in delivery and quality of cardiac care, and others as reported in the
23 QUALIFY international registry⁴⁸⁻⁵⁰.

1 In light of the known challenges in day-to-day practice of achieving 100% target doses of
2 combination therapies in HFrEF, our results emphasize that “some is better than none”. These
3 results add to that of studies in the SOLVD and CIBIS II trials, which showed the effects of low
4 dose enalapril⁵¹ or bisoprolol⁵² as single therapy. The TRED-HF trial⁵³ showed that withdrawal
5 of treatment studied the effect of evidence-based medical treatment withdrawal. All studies show
6 that patients already benefit from small doses of guideline-directed medical therapies. Thus,
7 initiating and maintaining guideline-directed medical therapies in patients with HFrEF remains a
8 quintessential aim in the management of these patients, even when target dose is not reached.
9
10 However, how do we manage dose titration in cases where full target doses of combination drugs
11 cannot be achieved (for instance when blood pressure is borderline)? Our results suggest that up-
12 titration to even sub-target doses of both ACEi/ARBs and β -blockers was associated with better
13 outcomes than full up-titration to 100% target doses of a single drug class (with either none or
14 very low doses of the other drug class). This is not to say that attempts at up-titration are not
15 important in real world practice; on the contrary we showed that achievement of higher doses of
16 both guideline-recommended drug classes was associated with reduction in composite outcomes
17 of death and HF hospitalization, consistent with prior trial evidence comparing lower versus
18 higher doses of guideline-directed medical therapies. In the ATLAS trial¹⁴, treatment with high
19 (32.5 to 35mg) vs low (2.5 to 5mg) daily doses lisinopril was associated with a non-significant
20 8% lower hazard of death but a significant 12% lower risk of all-cause death or hospitalization,
21 and 24% fewer hospitalizations for HF. Similar findings were found in the HEAAL trial, with the
22 use of low dose (50mg) vs. high dose (150mg) losartan¹⁶. In both trials, symptomatic
23 hypotension/syncope and renal insufficiency, and hyperkalaemia (only in HEAAL trial), were

1 more prevalent in the high dose group. The Multicenter Carvedilol Heart Failure Dose
2 Assessment (MUCHA) trial⁵⁴ was undertaken to establish the efficacy and safety of two doses
3 (low-5mg/day; high-20mg/day) of long-term carvedilol vs. placebo, in Japanese patients with HF
4 and LVEF \leq 40%. There was no statistical difference in outcomes between the high and low dose
5 of carvedilol. High (\geq 25 mg/day) vs. low dose ($<$ 25 mg/day) carvedilol equivalents in HF-
6 ACTION also conferred similar benefit for all-cause mortality and CV outcomes, although high
7 dose was superior (albeit with marginal significance) for a composite outcome of all-cause
8 mortality or HF hospitalization^{38,39}. Our results build on these prior trials and suggest that when
9 faced with the clinical conundrum of up-titrating both drugs versus up-titrating only one of the
10 drugs to maximal target doses, the former may be a preferable approach. Furthermore, we
11 observed that up-titrating β -blockers to 100% GRTD was associated with mortality benefit, even
12 when doses of ACEi/ARB were still sub-target. As a cautionary note, the guidelines advised slow
13 uptitration of β -blockers due to a possible transient HF worsening during the first 2 weeks after
14 upstart with β -blockers.

15

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

23

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

9

10 **Conclusions**

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

20

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23

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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 $\geq 100\%$ 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 $\geq 100\%$ 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 $\geq 100\%$ recommended treatment dose of ACEi/ARB and β -blocker dose;