# **Comparative National Prescriptive and Dosimetric Characteristics of Beta-Blocker Therapy in Asian Heart Failure Patients**

**Abstract**

Beta-blocker therapy remains a cornerstone of heart failure (HF) management, but its role in Asian populations is shaped by unique pharmacogenomic and economic factors. Registry data show prescription rates ranging from 61% in Indonesia to 91% in Japan, with consistently favorable outcomes despite markedly lower achieved doses compared to Western cohorts. Japanese patients, for example, attain equivalent survival and functional benefits at one-third of U.S. target doses, underscoring the need for region-specific dosing strategies. Across HF phenotypes, beta-blockers reduce mortality and hospitalization with no significant differences in adverse event rates among agents, and lower discontinuation rates in Asian cohorts suggest superior tolerability. Combination therapy with SGLT2 inhibitors, such as dapagliflozin, yields additive benefits, as efficacy persists regardless of background beta-blocker use. These findings support individualized therapy in Asia, highlighting the importance of integrating pharmacogenomics, health system capacity, and comorbidities into clinical decision-making.

**Keywords:** heart failure, beta-blockers, Asia, pharmacogenomics, SGLT2 inhibitors, dosing strategies

**Introduction**

Heart failure (HF) represents a growing public health burden across Asia, with prevalence estimates exceeding 60 million globally and steadily rising in low- and middle-income countries. Mortality and hospitalization rates remain unacceptably high, underscoring the importance of optimizing guideline-directed medical therapy (GDMT). Among pharmacologic options, β-blockers have consistently demonstrated mortality and morbidity benefits in patients with reduced ejection fraction (HFrEF), making them a cornerstone of contemporary management. In contrast, their role in patients with mid-range (HFmrEF) and preserved ejection fraction (HFpEF) is less clearly established and use in these phenotypes often reflects comorbidity-driven rather than HF-specific indications. Despite robust evidence for β-blockers in HFrEF, clinical practice across Asia is heterogeneous. Registry data show prescription rates ranging from 61% in Indonesia to 91% in Japan, with intermediate adoption in countries such as China (84%) and Southeast Asian nations (~70%). Economic stratification exerts a profound influence: higher-income countries such as Japan, Korea, and Singapore report greater uptake of dual therapy with ACEi/ARB and β-blockers, while lower-income nations lag in both frequency and dosing intensity. These disparities highlight the need to examine prescribing patterns through the lens of regional health systems, affordability, and drug availability. Knowledge gaps remain regarding both dose selection and clinical outcomes. Japanese cohorts achieve equivalent improvements in left ventricular function and survival despite receiving only one-third of U.S. target doses, raising questions about pharmacogenomic influences such as CYP2D6 metabolism and β-adrenergic receptor polymorphisms. Whether such differences extend to HFmrEF and HFpEF populations—where β-blocker use is already variable—remains unresolved. Furthermore, concerns about tolerability in underweight or elderly Asian patients, particularly with respect to hypotension and bradycardia, emphasize the importance of population-specific titration strategies. This study therefore evaluates β-blocker use in Asian HF populations, with attention to dosing heterogeneity, outcomes, and interaction with newer therapies such as SGLT2 inhibitors. By contrasting national patterns, highlighting pharmacogenomic considerations, and exploring phenotype-specific responses, we aim to clarify the rationale for individualized therapy and identify areas where Asian practice diverges from Western standards.

## **Prescriptive Patterns Among Asian Populations with HFmrEF and HFpEF**

Prescriptive practices for beta-blocker therapy across Asian territories exhibit marked heterogeneity, with substantive disparities in both adoption frequencies and dosing methodologies relative to Western therapeutic frameworks. Such regional variation necessitates systematic investigation to optimize treatment paradigms for heart failure patients presenting with mid-range ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) phenotypes. The ASIAN-HF registry data reveals pronounced geographic disparities in beta-blocker utilization throughout the region. Indonesia demonstrates the most conservative adoption patterns at 61% [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext), whereas Japan exhibits remarkably elevated usage frequencies approaching 91% [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext). Intermediate adoption patterns emerge across other territories—China reports 84.2% utilization among hospitalized HFrEF patients [[5]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11153617/), Southeast Asian nations demonstrate 70.2% overall usage [[6]](https://www.scienceopen.com/hosted-document?doi=10.15212/CVIA.2024.0026), and South Korea maintains prescription frequencies exceeding 65% [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext).

Economic stratification exerts considerable influence upon prescriptive behaviors. High-income territories including Singapore (71%), Hong Kong (70%), Korea (65%), and Japan (63%) demonstrate enhanced propensity for dual first-line therapeutic approaches combining ACE inhibitors or ARBs with beta-blockers compared to lower-income nations [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext). This economic stratification engenders treatment disparities with potential prognostic implications.

Regional heterogeneity extends beyond elementary prescription frequencies. Among HFpEF populations, where evidentiary support for beta-blocker efficacy remains less established, prescription rates nonetheless achieve 78.9% across Southeast Asian countries [6]. The DELIVER trial cohort indicates approximately 80% of HFmrEF and HFpEF patients receive beta-blockers [[3]](https://www.sciencedirect.com/science/article/pii/S2213177923006157), predominantly for comorbid conditions rather than heart failure management *per se*.

### **Carvedilol-Equivalent Dosing Strategies Among Asian Cohorts**

Carvedilol (37%), bisoprolol (30%), and metoprolol (11%) comprise the most frequently prescribed beta-blockers across Asian territories [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext). Administered dosages consistently fall below guideline recommendations, however. Median prescribed dosages across Asian cohorts achieve merely 25% of recommended targets, with 65% of patients receiving less than half the guideline-recommended dosage [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext). This pattern of reduced dosing may represent an appropriate therapeutic strategy for Asian populations. Japanese patients demonstrate equivalent clinical effectiveness compared to American counterparts despite receiving lower carvedilol dosages [[7]](https://www.ahajournals.org/doi/10.1161/circ.146.suppl_1.13725). Initial carvedilol dosing in Japanese patients averages 4.3 mg daily compared to 14.5-19.1 mg daily among American patients, while one-year dosages average 11.2 mg daily versus 30.9-34.5 mg daily [[7]](https://www.ahajournals.org/doi/10.1161/circ.146.suppl_1.13725). Pharmacogenetic considerations have influenced regional guideline development. Japanese national guidelines recommend lower target dosages (20 mg daily) compared to American guidelines (50 mg daily) [[8]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10919845/). Despite these reduced dosages, Japanese patients demonstrate comparable improvements in left ventricular ejection fraction and heart rate reduction [[7]](https://www.ahajournals.org/doi/10.1161/circ.146.suppl_1.13725). Asian patients appear to achieve clinical benefits at lower dosages while potentially minimizing adverse effects. Regional dosing heterogeneity extends beyond initial recommendations. Malaysia and Thailand administer the highest beta-blocker dosages throughout Asia, whereas Japan, despite elevated uptake (91%), maintains the lowest dosages with 41% of patients receiving less than 25% of guideline-recommended quantities [[4]](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30306-1/fulltext).

### **Alternative Therapeutic Indications: Hypertension, Coronary Disease, and Atrial Fibrillation**

Beta-blockers serve multiple therapeutic functions beyond heart failure management among Asian populations. ESC guidelines indicate 80% of HFpEF patients receive beta-blockers for indications other than frank heart failure [[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11802620/). Alternative therapeutic applications encompass:

1. **Coronary Artery Disease**: Beta-1 selective agents (atenolol, metoprolol, bisoprolol) reduce heart rate and blood pressure, diminishing myocardial oxygen demand and attenuating future myocardial infarction risk [[10]](https://bnrc.springeropen.com/articles/10.1186/s42269-024-01208-z).
2. **Hypertensive Management**: Beta-blockers maintain relevance as initial therapeutic options for hypertensive patients with cardiovascular comorbidities [[10]](https://bnrc.springeropen.com/articles/10.1186/s42269-024-01208-z), although their role as first-line therapy has diminished within contemporary guidelines.
3. **Atrial Fibrillation**: Beta-blockers facilitate heart rate regulation, reduce cardiac strain, and may contribute to thromboembolic prevention and stroke risk reduction [[10]](https://bnrc.springeropen.com/articles/10.1186/s42269-024-01208-z).

Given these multiple indications, beta-blocker utilization frequently persists regardless of heart failure classification. This practice aligns with emerging evidence suggesting potential benefits among HFpEF patients. One nationwide investigation identified statistically significant survival improvement following three years of beta-blocker therapy among HFpEF patients [[9]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11802620/), supporting continued utilization as guideline recommendations continue to evolve.

## **Mortality Reduction and Cardiovascular Event Prevention**

Contemporary investigations examining mortality outcomes provide evidence supporting beta-blocker utilization among Asian heart failure populations. Clinical trials demonstrate consistent benefits across multiple cardiovascular endpoints, with profound implications for therapeutic strategies within these populations. Beta-blocker therapy produces marked reductions in adverse outcomes among Asian heart failure patients across multiple investigational frameworks. The primary composite of worsening heart failure events or cardiovascular death correlates inversely with beta-blocker utilization, yielding a hazard ratio of 0.79 (95% CI: 0.68-0.92) [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007). After adjustment for baseline demographics and established prognostic variables, this protective effect persists with a hazard ratio of 0.70 (95% CI: 0.60-0.83) [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007). Peritoneal dialysis patients represent a particularly compelling cohort for beta-blocker investigation. Among this population, beta-blocker prescription associates with a 43% reduction in adjusted hazard ratio for heart failure death (95% CI: 0.36–0.89; p = 0.013) [[11]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10913941/). Early beta-blocker administration yields even more dramatic results, reducing in-hospital composite endpoints by 58% (RR: 0.42; 95% CI: 0.30–0.58; p < 0.001) and in-hospital all-cause mortality by 57% (RR: 0.43; 95% CI: 0.31–0.61; p < 0.001) [[12]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11399533/). Non-cardioselective beta-blockers demonstrate superior mortality reduction in certain Asian cohorts, with cardiovascular mortality decreasing both in unadjusted models (HR: 0.36; 95% CI: 0.18–0.73; p = 0.004) and following statistical adjustment (HR: 0.37; 95% CI: 0.19–0.73; p = 0.005) [[13]](https://onlinelibrary.wiley.com/doi/10.1002/ehf2.13489). Competing risk analytical frameworks further substantiate beta-blocker benefits among Asian populations. When incorporating competing risk events, the hazard ratio for primary composite outcomes remains 0.68 (95% CI: 0.58-0.79) [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007). Patients receiving beta-blockers maintain a lower cumulative risk for heart failure-related mortality compared to non-users even after accounting for competing risk events (p = 0.007) [[11]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10913941/). Regional heterogeneity within Asia reveals stark disparities in outcomes. Southeast Asian patients experience higher risk profiles, with death or hospitalization rates reaching 25.4% (345 per 1000 person-years) compared to 4.5% (55 per 1000 person-years) among South Asian populations (p < 0.001) [[14]](https://onlinelibrary.wiley.com/doi/full/10.1002/ejhf.1227). Ethnic stratification demonstrates that Malay patients face worse outcomes relative to Chinese patients (HR 2.13, 95% CI 1.34–3.37) [[14]](https://onlinelibrary.wiley.com/doi/full/10.1002/ejhf.1227).

**Table 1: Prescription Rates of Beta-Blocker in Asian Countries**

|  |  |  |
| --- | --- | --- |
| **Country** | **Beta-Blocker** | **Rx rate (as percentage) Notes** |
| Japan | 91% | Beta-blockers highly adopted, particularly carvedilol. |
| China | 84.2% | Good uptake among hospitalized patients who have HFrEF |
| South Korea | 65% | Moderate uptake of patients with HF in hospitals. |
| Indonesia | 61 percent Low | probably because of economic and healthcare access differences. |
| Singapore | 71% | Represents practice of dual therapy by a high-income country. |

*Source: ASIAN-HF Registry, 2024*

Beta-blocker therapy extends beyond mortality benefits to encompass total heart failure event reduction among Asian populations. Patients receiving beta-blockers demonstrate reduced risk for heart failure events, cardiovascular death, and total heart failure events across crude, covariate-adjusted, and propensity score–based analytical models [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007). Cumulative survival probabilities illustrate these benefits with striking clarity:

1. Beta-blocker users: 89.7% survival at 3 years, 86.5% at 5 years
2. Non-users: 77.4% survival at 3 years, 75.3% at 5 years [[11]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10913941/).

The relationship between beta-blocker benefits and left ventricular ejection fraction (LVEF) merits particular attention. Beta-blocker associations with clinical outcomes demonstrate consistency regardless of LVEF categorization (LVEF ≤49% versus ≥50%), with interaction p-values exceeding 0.47 [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007). This finding suggests that beta-blocker benefits transcend traditional heart failure classifications, providing therapeutic value across the spectrum of ventricular dysfunction.

## **SGLT2 Inhibitors and Beta-Blocker Combination Therapy**

SGLT2 inhibitors like dapagliflozin represent a contemporary pharmaceutical development constructed to address metabolic and cardiovascular pathophysiology through novel mechanisms. The interaction between these agents and established beta-blocker therapy demands rigorous examination, particularly when considering potential synergistic effects or therapeutic conflicts in Asian patient populations. The DELIVER trial, comprising 6,263 patients with heart failure and left ventricular ejection fraction exceeding 40%, furnishes essential data regarding combination therapeutic strategies. Among study participants, 83% received concurrent beta-blocker therapy, with notable regional variations [[15]](https://pubmed.ncbi.nlm.nih.gov/37767674/). Dapagliflozin demonstrated consistent therapeutic efficacy irrespective of simultaneous beta-blocker utilization. The primary composite endpoint of cardiovascular death or worsening heart failure showed comparable reduction in patients receiving beta-blockers (HR: 0.82; 95% CI: 0.72-0.94) and those without beta-blocker therapy (HR: 0.79; 95% CI: 0.61-1.03) [[15]](https://pubmed.ncbi.nlm.nih.gov/37767674/). The interaction p-value of 0.85 substantiates the statistical consistency of these benefits across both therapeutic groups [[15]](https://pubmed.ncbi.nlm.nih.gov/37767674/). Beta-blocker therapy is associated with diminished risk for the composite outcome (adjusted HR: 0.70; 95% CI: 0.60-0.83) [[16]](https://www.thecardiologyadvisor.com/news/%CE%B2-blocker-use-does-not-affect-dapagliflozin-safety-or-efficacy-in-hfpef-or-hfmref/), suggesting these pharmaceutical interventions operate through complementary rather than competing mechanisms.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) assessments revealed improvements with dapagliflozin therapy independent of background beta-blocker status. At 8 months, multiple domains demonstrated statistically significant enhancements at the 0.01 confidence level:

1. Total Symptom Score: 2.4-point improvement versus placebo (p<0.001)
2. Physical Limitations Score: 1.9-point improvement versus placebo (p<0.001)
3. Clinical Summary Score: 2.3-point improvement versus placebo (p<0.001)
4. Overall Summary Score: 2.1-point improvement versus placebo (p<0.001) [[17]](https://www.jacc.org/doi/10.1016/j.jacc.2022.11.006)

**Table 2: Dosages and Therapeutic Recommendations for Asian Patients**

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| --- | --- | --- | --- | --- |
| Therapy | Condition | Typical guideline class (ACC/AHA/ESC) | Typical starting dose → common trial/target dose | Asian guideline/practice differences (class / dosing / notes) |
| β-blockers (evidence agents: bisoprolol, carvedilol, metoprolol succinate) | HFrEF (EF ≤40%) | Class I, LOE A — recommended as foundational therapy [29]. | Carvedilol: start 3.125 mg BID, uptitrate (6.25 → 12.5 → 25 mg BID as tolerated). Bisoprolol: start 1.25–2.5 mg daily → target 10 mg daily. Metoprolol succinate (XL): start 12.5–25 mg daily → target 200 mg daily. (Targets are those used/endorsed in trials/guidelines) [30]. | Asian guidelines also endorse β-blockers as core therapy for HFrEF (class I), but in practice targets are often lower and titration slower because of lower average body weight, hypotension/bradycardia risk, and comorbidity burden. Many Asian consensus documents emphasize “titrate as tolerated” and accept lower achieved doses in real-world practice [31]. |
| β-blockers | HFmrEF (EF ~41–49%) | Weak/moderate evidence; often consider or IIa/IIb depending on guideline and comorbidities. [29]. | If used, start and titrate same agents/doses as HFrEF but expectation of benefit is lower, and evidence is less definitive; use mainly for rate control (AF) or ischemic disease [29]. | Asian practice mirrors international guidance: β-blockers often used if indicated (AF, ischemia); routine mortality benefit is not established, so usage varies by country/clinic [31]. |
| SGLT2 inhibitors (dapagliflozin, empagliflozin) | HFrEF | Class I for chronic HFrEF (benefit on CV death & HF hospitalization) — recommended irrespective of diabetes status [29]. | Doses: Dapagliflozin 10 mg PO once daily; Empagliflozin 10 mg PO once daily (trial dose and guideline dose). Initiate on top of GDMT; minimal titration — usually start 10 mg daily if no contraindication. ACC/clinical pocket guides echo 10 mg daily dose [32]. | In Asia, guidelines increasingly endorse SGLT2i for HFrEF (many Asian societies now include them as part of GDMT). However, uptake is more variable due to regulatory timing, cost/reimbursement, and local formulary access; clinicians may delay initiation or reserve for selected patients. Some local guidance emphasizes renal function thresholds and monitoring [30]. |
| SGLT2 inhibitors | HFmrEF | IIa (reasonable to consider) in many recent guidelines based on DELIVER/EMPEROR-Preserved subgroup analyses/meta-analyses [32]. | Same dose: 10 mg once daily (dapagliflozin/empagliflozin). Benefit mainly on HF hospitalization; mortality signal less consistent [32]. | Asian guidance tends to be cautious but favorable — many Asia-Pacific statements say SGLT2i may be used in HFmrEF/HFpEF (often phrased “in selected patients”); economic/access issues may limit real-world use [30]. |
| SGLT2 inhibitors | HFpEF | Class IIa (growing evidence) in many modern guidelines after DELIVER/EMPEROR-Preserved — recommended to reduce HF hospitalization (and possibly CV death in some analyses) [32]. | Dose: dapagliflozin 10 mg PO daily; empagliflozin 10 mg PO daily. Start if eGFR above local threshold (product labels and guidance differ; still used down to modest eGFR ranges for HF benefit). Monitor volume status, renal function, and risk of genitourinary infections [33]. | Asian recommendations increasingly align with global guidance in wording (Class IIa / reasonable to consider), but implementation varies by country—cost, reimbursement, and timing of regulatory approvals are the main barriers. Also, clinicians commonly watch for low blood pressure/volume status in smaller/older patients and will start more cautiously [30]. |

These improvements emerged within one month and amplified throughout the observation period [[17]](https://www.jacc.org/doi/10.1016/j.jacc.2022.11.006). A greater proportion of patients receiving dapagliflozin achieved clinically meaningful KCCQ improvements regardless of concurrent beta-blocker therapy [[17]](https://www.jacc.org/doi/10.1016/j.jacc.2022.11.006).

Safety analyses reveal no reported pharmacodynamic interference between beta-blockers and dapagliflozin. The DAPA-HF investigation demonstrated that dapagliflozin reduced the combined risk of cardiovascular death and heart failure hospitalization by 26%, with cardiovascular mortality alone declining by 18%—benefits that remained unaffected by concomitant beta-blocker utilization [[18]](https://pmc.ncbi.nlm.nih.gov/articles/PMC7327531/). Adverse events were equally prevalent in dapagliflozin and placebo groups irrespective of background beta-blocker therapy (all interaction p-values ≥0.07) [[16]](https://www.thecardiologyadvisor.com/news/%CE%B2-blocker-use-does-not-affect-dapagliflozin-safety-or-efficacy-in-hfpef-or-hfmref/). Comprehensive safety assessments revealed no significant differences at the 0.05 confidence level between treatment groups regarding serious adverse events, volume depletion symptoms, acute kidney injury, or hyperkalemia rates [[19]](https://pmc.ncbi.nlm.nih.gov/articles/PMC9301591/). Although tentative, this evidence supports further research into the clinical efficacy of co-administration of beta-blockers and SLGT2 inhibitors heart failure management in Asian populations.

## **Safety Profiles and Adverse Event Patterns Among Asian Heart Failure Patients**

Safety evaluation of beta-blocker therapy among Asian populations demonstrates distinctive adverse event profiles that merit careful consideration. These patterns inform clinical decision-making processes and provide essential context for treatment optimization. Bradycardia and hypotension constitute the predominant adverse reactions associated with beta-blocker therapy, totaling 3,778 and 3,264 reported cases respectively across different agents [[20]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11566443/). The distribution of bradycardia incidence reveals marked variation by specific drug type. Metoprolol accounts for the highest proportion (29.9%) of bradycardia cases [[20]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11566443/). Bisoprolol emerges as the second most frequent contributor to bradycardia (23.9%), while carvedilol occupies second position for both hypotension and dizziness manifestations at 18.6% and 26.3% respectively [[20]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11566443/). Clinical experience demonstrates bradycardia incidence ranging from 0.4% to 12% among beta-blocker recipients, contrasted with 0-5% in placebo cohorts [[21]](https://pmc.ncbi.nlm.nih.gov/articles/PMC5122500/). Notably, asymptomatic bradycardia during treatment typically does not warrant therapeutic discontinuation according to randomized controlled trial evidence [[21]](https://pmc.ncbi.nlm.nih.gov/articles/PMC5122500/). This finding suggests that heart rate reduction alone should not prompt treatment cessation without accompanying symptomatic manifestations. Japanese clinical investigations reveal superior titration success rates for bisoprolol, with 90.3% of patients achieving maintenance dosing compared to 85.7% for carvedilol [[22]](https://pubmed.ncbi.nlm.nih.gov/23559359/). More striking is the observation that Japanese patients exhibited substantially lower discontinuation and dose reduction rates relative to United States populations, with a relative rate of 0.406 (0.086 vs. 0.212, 95% CI: 0.181 to 0.911, p = 0.035) [[8]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10919845/). Discontinuation patterns differ according to specific agent characteristics. Bisoprolol discontinuation occurred in 2.6% of cases, predominantly attributed to hypotensive episodes, while dose modifications were necessary in 18.4% of patients [[8]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10919845/). Carvedilol presented a contrasting profile, requiring dose reductions in merely 2.2% of cases, primarily due to bradycardia and hypertensive heart disease complications [[8]](https://pmc.ncbi.nlm.nih.gov/articles/PMC10919845/). The absence of marked differences in serious adverse events between beta-blocker types among Asian populations represents a crucial clinical finding. Event-free survival rates for the composite outcome of cardiovascular death or heart failure hospitalizations reached 92.4% with bisoprolol and 94.7% with carvedilol—a statistically insignificant difference at the 0.05 confidence level [[22]](https://pubmed.ncbi.nlm.nih.gov/23559359/). Hospital-based adverse events, including bradyarrhythmias and hypotensive episodes, demonstrated no significant differences between early beta-blocker administration and control groups (RR: 0.75; 95% CI 0.52–1.09; p = 0.13) [[12]](https://pmc.ncbi.nlm.nih.gov/articles/PMC11399533/). Treatment discontinuation rates remained comparable with concurrent dapagliflozin therapy regardless of beta-blocker utilization [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007).

## **Guideline Discordance and the Pursuit of Individualized Therapy**

Contemporary guideline recommendations for beta-blocker therapy demonstrate profound inconsistencies across major cardiology organizations, a situation that demands judicious clinical interpretation rather than blind adherence. The European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) present starkly divergent approaches to HFpEF management. The AHA/ACC/HFSA guidelines explicitly discourage beta-blocker utilization for HFpEF treatment [[1]](https://www.jacc.org/doi/10.1016/j.jchf.2023.09.007), yet paradoxically endorse these agents for HFmrEF patients based upon meta-analytical evidence demonstrating reduced cardiovascular mortality [[23]](https://www.sciencedirect.com/science/article/pii/S2666602221000513). The ESC guidelines, perhaps more honestly, offer no definitive recommendations regarding beta-blocker therapy for HFpEF [[24]](https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2024/04/16/15/08/contemporary-american-and-european). This regulatory ambiguity is troublesome given the body of evidence supporting beta-blocker efficacy across the heart failure spectrum. The reluctance to provide clear guidance likely stems from the heterogeneous nature of HFpEF itself—a syndrome encompassing diverse pathophysiological mechanisms that resist uniform therapeutic approaches.

### Cardioselective beta-blockers demonstrate markedly superior clinical outcomes compared to non-selective agents in Asian populations. Rigorous investigations reveal that cardioselective formulations associate with reduced all-cause mortality (HR: 0.93; 95% CI: 0.89-0.96), major adverse cardiovascular events (HR: 0.96; 95% CI: 0.93-0.998), heart failure hospitalizations (HR: 0.84; 95% CI: 0.78-0.91), and pulmonary complications (HR: 0.94; 95% CI: 0.90-0.98) [[25]](https://pubmed.ncbi.nlm.nih.gov/35135688/). This therapeutic advantage derives from beta-1 selectivity, which circumvents bronchospasm risk among patients with concurrent respiratory conditions [[26]](https://www.sciencedirect.com/science/article/pii/S0025619621006224). Treatment individualization based upon patient-specific comorbidity profiles yields optimal clinical outcomes [[27]](https://www.jacc.org/doi/10.1016/j.jchf.2021.06.011). Several key considerations merit emphasis:

1. Chronic Obstructive Pulmonary Disease: Beta-1 selective agents (bisoprolol, metoprolol, nebivolol) prevent exacerbation of respiratory symptoms while preserving cardiovascular benefits [[28]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8468030/).
2. Diabetes Mellitus: Carvedilol and bisoprolol warrant preference given their neutral effects upon glycemic control profiles [[28]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8468030/).
3. Atrial Fibrillation: Despite conflicting evidence from randomized trials, real-world observational data suggests prognostic advantages independent of rhythm status [[28]](https://pmc.ncbi.nlm.nih.gov/articles/PMC8468030/).

The complexity of these considerations underscores why algorithmic approaches to beta-blocker selection often prove inadequate. Clinical judgment, informed by population-specific evidence and individual patient characteristics, remains paramount.

### **HFmrEF and HFpEF: Distinct Therapeutic Rationales**

In HFrEF, β-blockers are universally recommended as Class I therapy given their robust mortality benefit [1,2]. In HFmrEF and HFpEF, however, utilization is less consistent and often comorbidity driven. In the ASIAN-HF registry, nearly 80% of HFpEF patients received β-blockers, predominantly for atrial fibrillation, ischemic heart disease, or hypertension rather than heart failure per se [4,6]. Importantly, subgroup analyses demonstrate no significant interaction between LVEF strata and β-blocker outcomes (interaction p>0.47), suggesting benefit extends beyond classical HFrEF [1]. Nonetheless, heterogeneity in HFpEF pathophysiology complicates guideline recommendations, with U.S. guidelines discouraging routine use while ESC guidance remains non-committal [23,24]. Precision medicine approaches that differentiate comorbidity-driven versus HF-driven β-blocker use are warranted.

### **Dose Differences and Mechanistic Explanations**

A key observation is that Asian patients often achieve equivalent outcomes at substantially lower doses than their Western counterparts. Japanese cohorts initiate carvedilol at ~4.3 mg/day and maintain ~11.2 mg/day at one year, compared with 14.5–34 mg/day in the U.S. [7]. Despite these lower doses, survival and functional outcomes are comparable, with hazard ratios for composite endpoints consistently favoring β-blocker use (HR 0.70, 95% CI 0.60–0.83) [1]. Pharmacogenomic factors likely contribute: CYP2D6 polymorphisms prevalent in Asian populations alter carvedilol metabolism, and β-adrenergic receptor variants (e.g., ADRB1 Arg389Gly) may enhance receptor sensitivity [8]. These mechanisms provide biological plausibility for reduced dose requirements while minimizing adverse events.

### **Economic Stratification and Prescriptive Behavior**

Economic disparities across Asia strongly influence both β-blocker and SGLT2 inhibitor prescribing. High-income countries such as Japan, Korea, and Singapore more frequently employ dual therapy with ACEi/ARB and β-blockers, whereas lower-income nations such as Indonesia exhibit lower adoption and reduced dosing intensity [4]. Affordability, hospital policy, and formulary availability also shape dose titration strategies, with some hospitals avoiding higher doses due to monitoring costs or limited drug supply. These structural factors compound the pharmacogenomic differences, creating multi-layered heterogeneity in prescribing patterns.

### **Evidence from DELIVER and DAPA-HF in Asian Patients**

Large outcome trials provide reassuring evidence that reduced doses do not compromise efficacy when combined with contemporary therapy. The DELIVER trial enrolled ~25% Asian patients, and DAPA-HF ~22%, with subgroup analyses demonstrating no heterogeneity of effect by region [3,15,17]. Dapagliflozin reduced cardiovascular death or worsening HF irrespective of background β-blocker use (HR 0.82 with β-blockers vs. HR 0.79 without; interaction p=0.85) [15]. Similarly, DAPA-HF showed a 26% reduction in the composite endpoint and 18% reduction in cardiovascular mortality, unaffected by β-blocker co-administration [18]. These results confirm that β-blockers and SGLT2 inhibitors operate through complementary rather than antagonistic mechanisms.

**Mechanistic Rationale for Synergy**

SGLT2 inhibitors reduce preload and afterload via osmotic diuresis and natriuresis, improve myocardial energetics, and lower interstitial volume [15,17–19]. β-blockers, by contrast, reduce sympathetic drive, heart rate, arrhythmic risk, and ischemic burden [10,27]. These non-overlapping mechanisms explain why dapagliflozin maintained efficacy irrespective of β-blocker status, with additive rather than redundant benefits [15,18]. Together, these agents represent a rational foundation for combination therapy in precision medicine strategies.

### **Vulnerable Subgroups: Elderly and Underweight Patients**

Asian HF patients are often smaller in body size and older at presentation compared with Western cohorts, increasing susceptibility to bradycardia and hypotension. Registry data report bradycardia incidence of 0.4–12% in β-blocker users versus 0–5% in placebo [21]. Japanese studies further show superior tolerability, with lower discontinuation rates relative to the U.S. (RR 0.406, p=0.035) [8]. These findings highlight the need for cautious titration in underweight and elderly patients, frequent monitoring of renal function and electrolytes, and individualized dose ceilings that balance efficacy with tolerability [20,22].

### **Toward Precision Medicine in Asia**

The observed heterogeneity in dosing, outcomes, and economic access across Asia argues against a “one-size-fits-all” dosing paradigm. Instead, population-specific guidelines—such as the lower carvedilol targets in Japan (20 mg daily) compared with the U.S. (50 mg daily) [7,8]—may better reflect pharmacogenomic realities and clinical practice. Future trials should prioritize stratified analyses in Asian cohorts, incorporating pharmacogenomic, economic, and comorbidity data to inform individualized treatment algorithms. Ultimately, integrating β-blockers and SGLT2 inhibitors within precision medicine frameworks offers the opportunity to optimize survival and quality of life across diverse Asian populations.

## **Conclusion**

This study underscores the complexity of β-blocker therapy in Asian patients with heart failure, where prescriptive practices, dosing strategies, and clinical outcomes diverge from Western standards. Our findings support the continued role of β-blockers across the HF spectrum while emphasizing that regional pharmacogenomics, economic stratification, and comorbidity profiles shape both utilization and outcomes. Further research will be necessary to appropriately differentiate the therapeutic regimen for hypotensive and hypovolemic patients and those with comorbid advanced renal failure. Another avenue of further research concerns the precise biochemical mechanisms occasioned by the genetic drug metabolism signatures in Asian patients. Dapagliflozin maintains consistent efficacy irrespective of background beta-blocker utilization, suggesting these therapeutic modalities operate through complementary rather than competitive mechanisms. Such observations support combination therapy strategies that may yield superior outcomes compared to monotherapy approaches. Nonetheless, cardioselective beta-blockers demonstrate promise in Asian populations, especially when prescribed considerations account for comorbid conditions and left ventricular function. Future investigations should prioritize the refinement of population-specific dosing algorithms and combination therapy protocols, ultimately advancing precision medicine approaches that acknowledge both regional and individual patient characteristics in therapeutic decision-making.

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